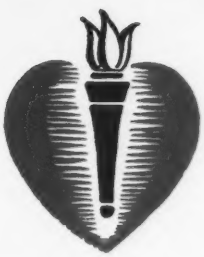
JULY 1956
VOL. XIV NO. 1

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



Annual Meeting of the American Heart Association
Cincinnati, Ohio, from October 26–31, 1956

Published by Grune & Stratton, Inc.

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

To help the kidneys

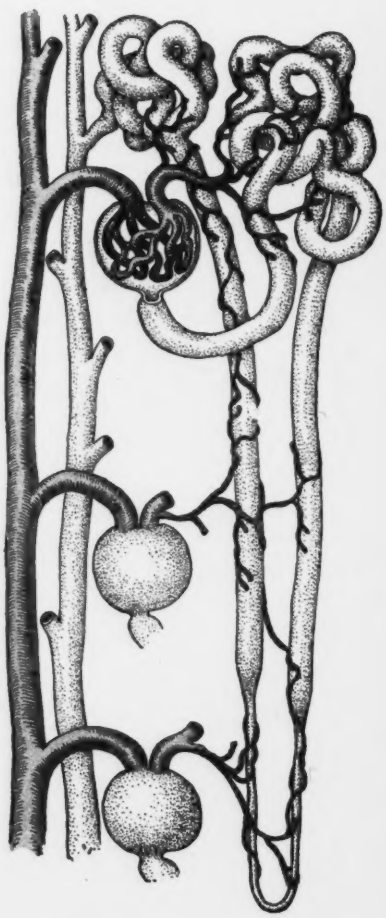
rid the body of excess fluid

SALYRGAN®-THEOPHYLLINE

Dependable mercurial-xanthine diuretic

—prevents reabsorption of water and sodium by the renal tubules.

Elimination of sodium as well as water decreases the body's capacity to retain fluid.



Parenteral administration (intramuscularly or intravenously) of Salyrgan-Theophylline dependably reduces edema and ascites in cardiovascular failure, nephrosis and hepatic cirrhosis.

Oral administration of Salyrgan-Theophylline tablets has become an established routine for interim diuresis — between parenteral administration — and for milder cases of edema and ascites. Patient response regulates the oral dosage.

SUPPLIED:

Ampuls **of 1 cc. and 2 cc.—boxes of 10, 25 and 100.**

Tablets **—bottles of 100, 500 and 1000.**

Another useful aid:

NEOCURTASAL®

Salt without Sodium

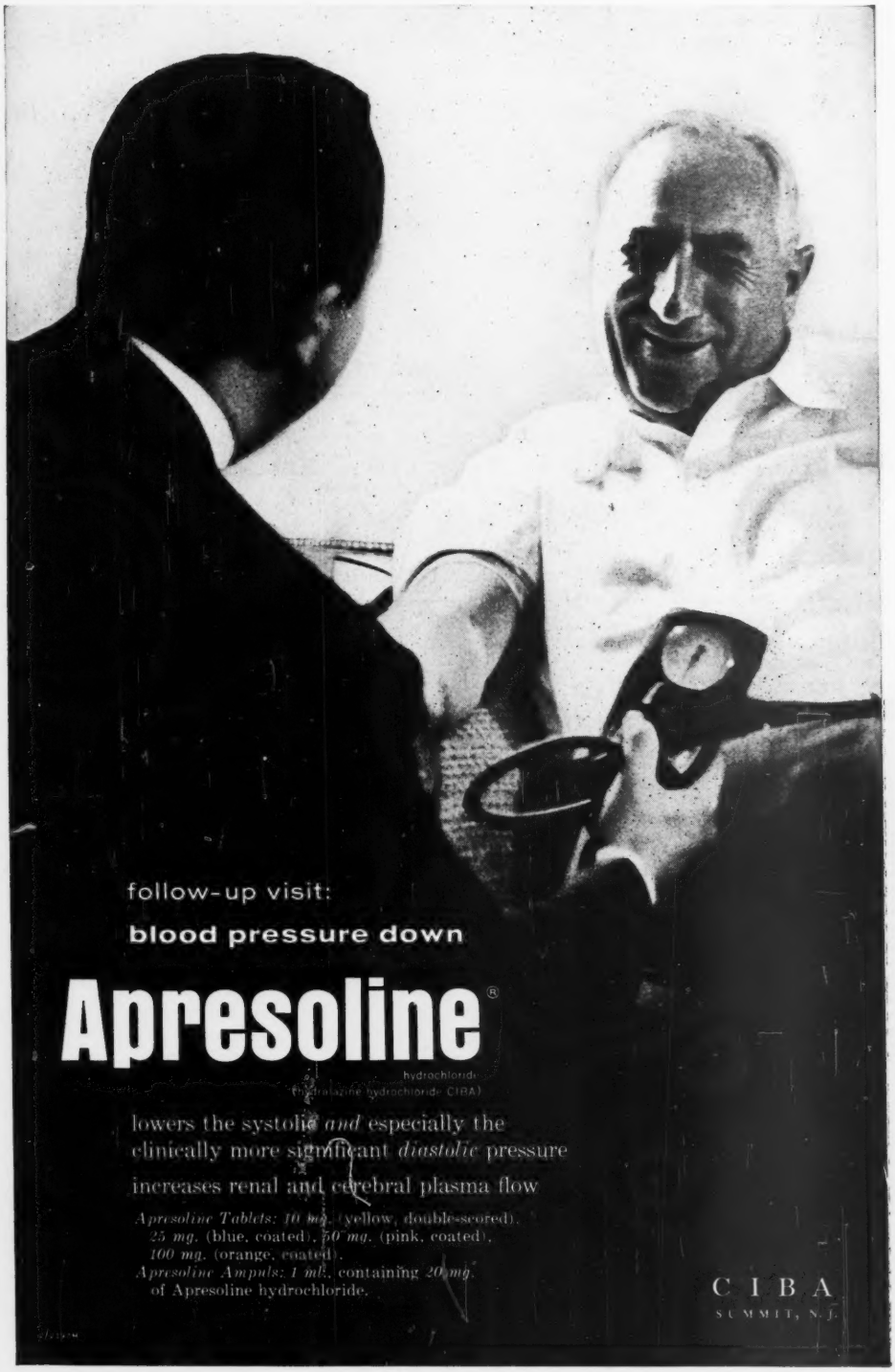
CONSTITUENTS: Potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate, potassium iodide (0.01%) and starch.

2 oz. shakers • 8 oz. bottles

Winthrop LABORATORIES

NEW YORK 18, N.Y. • WINDSOR, ONT.

Salyrgan (brand of mersalyl) and Neocurtasal, trademarks reg. U. S. Pat. Off.


follow-up visit:
blood pressure down
Apresoline®
hydrochloride
(hydralazine hydrochloride CIBA)
lowers the systolic *and* especially the
clinically more significant *diastolic* pressure
increases renal and cerebral plasma flow
Apresoline Tablets: 10 mg. (yellow, doublescored).
25 mg. (blue, coated). *50 mg.* (pink, coated).
100 mg. (orange, coated).
Apresoline Ampuls: 1 ml., containing *20 mg.*
of Apresoline hydrochloride.
CIBA
SUMMIT, N. J.

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

HERRMAN L. BLUMGART, M.D., Editor-in-Chief

330 Brookline Avenue, Boston 15, Mass.

EDITH E. PARRIS, Assistant Editor

ASSOCIATE EDITORS

EDGAR V. ALLEN, M.D. *Rochester, Minn.*

SAMUEL BELLET, M.D. *Philadelphia, Pa.*

PAUL M. ZOLL, M.D. *Boston, Mass.*

Correspondence concerning *editorial* matters should be addressed to the Editor-in-Chief, at the above address. All communications concerning *business* matters should be addressed to Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, N. Y.

Subscription rates, $13.00 per year within the United States and Canada; $14.00 per year elsewhere. Single copies, $2.00; foreign, $2.50; October 1955, $3.50. A combination subscription with *Circulation Research* is available at $19.00 per year within the United States and Canada, $22.50 per year elsewhere. Subscriptions are accepted on a calendar year basis.

Agents for Great Britain, H. K. Lewis & Co., Ltd., 136 Gower Street, London, W.C.1, England.

Published monthly at Mount Royal & Guilford Avenues, Baltimore, Md. Entered as second-class matter at the Post Office, Baltimore, Md., Jan. 9, 1950, under the Act of March 3, 1879.

Original Communications. Manuscripts for publication, letters and all other editorial communications should be addressed to the Editor-in-Chief, at the above address. Articles are accepted for publication on the condition that they are contributed solely to this journal.

Manuscripts. Duplicate manuscripts, tables and illustrations should be submitted to facilitate selection and processing of papers. Manuscripts should be typewritten on good quality paper, one side of the page only, with double or triple spacing and liberal margins. They should include the authors' degrees and hospital and academic affiliations (for use on the "Contributors" page), and an address for mailing proofs. References to the literature should be compiled at the end of the article in numerical sequence, the style of this journal being observed regarding the full amount of material to be included in each bibliographic entry, the order of material, capitalization and punctuation. If a "Personal Communication" is listed in the bibliography, a letter must be submitted in which the direct quotation is given with the signature of the original author.

A foreword not to exceed 100 words should also be submitted with the manuscript. This foreword should serve primarily as an orientation for the reader by stating the general problem, the purpose of the study, and the approach or lines of investigation utilized. The results and conclusions should generally be reserved for the Summary.

Illustrations and Tables. Position of figures and tables in the text should be marked on manuscript. *Circulation* uses arabic rather than roman numbering. Figures should carry their number and the author's name on the back; figure legends should be compiled in a separate list. To ensure clear reproduction, all copy for zinc cuts, including pen drawings and charts, should be prepared with black india ink, and a black ribbon should be used for typewritten material; for halftone work, good photographic prints or the original drawings should be supplied. Special arrangements must be made with the editor for printing of color plates, elaborate tables or an excessive number of illustrations.

Reprints. Reprints of articles will be furnished to contributors when ordered in advance of publication An order form, showing cost of reprints, is sent with proofs. Individual reprints of an article can usually be obtained by writing directly to its author at the address given on the "Contributors" page of that issue.

Exchanges. Contributions, letters, exchanges, reprints and all other communications relating to the Abstracts Department of *Circulation* should be sent to the Editor-in-Chief at the above address. Writers on subjects which are related in any way to cardiovascular disease are requested to place this address on their permanent mailing list.

Book Reviews. Books and monographs treating specifically of the same subject matter as this Journal will be reviewed as space is available. Send books for review to the Editor-in-Chief, at the above address.

Business Communications. Send all communications regarding advertising, subscriptions, change of address, etc., to the Publisher, at the address listed below. *Remittance for subscriptions* should be made by check, draft, post office or express money order to the Publisher. Members of the American Heart Association should make subscription arrangements with the Association. The Publisher should be advised of *change of address* about thirty days before date of issue, with both the subscriber's old and new address given. *Advertising space* is given only to articles of known scientific value. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.

COPYRIGHT 1956, GRUNE & STRATTON, INC.

381 FOURTH AVENUE, NEW YORK 16, N. Y.

Depropanex.®

DEPROTEINATED PANCREATIC EXTRACT

promptly relieves smooth muscle spasm

MAJOR ADVANTAGES: Physiologic relief of pain. Non-narcotic. Non-toxic.

You can relieve spasm in 3 minutes with DEPROPANEX[1]

DEPROPANEX, by relieving smooth muscle spasm, is valuable in ureteral, renal and biliary colic and in various urologic instrumental procedures.

Intermittent claudication is markedly improved with DEPROPANEX.[2,3] DEPROPANEX is also valuable in the control of paralytic ileus following abdominal surgery.

That DEPROPANEX has "beneficial effect... throughout the post-operative period has been convincingly demonstrated."[4] There is less nausea, little need for intravenous fluids, for nasal suction or enemas.[4]

Dosage of DEPROPANEX is 2 to 5 cc. It is *supplied* in 10 cc. and 30 cc. rubber-capped vials.

References: 1. South. M. J. 31:233 (March) 1938. 2. Bull. New York Acad. Med. 19:478 (July) 1943. 3. Am. Heart J. 18:425 (Oct.) 1939. 4. Minnesota Med. 33:1102 (Nov.) 1950.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

EDITOR-IN-CHIEF

HERRMAN L. BLUMGART, *Boston, Mass.*
EDITH E. PARRIS, *Assistant Editor*

EDITORIAL BOARD

E. COWLES ANDRUS, *Baltimore, Md.*
BENJAMIN M. BAKER, *Baltimore, Md.*
JANET S. BALDWIN, *New York, N. Y.*
GEORGE E. BURCH, *New Orleans, La.*
HOWARD B. BURCHELL, *Rochester, Minn.*
J. SCOTT BUTTERWORTH, *New York, N. Y.*
A. C. CORCORAN, *Cleveland, Ohio*
ANDRÉ COURNAND, *New York, N. Y.*
THADDEUS S. DANOWSKI, *Pittsburgh, Pa.*
CHARLES T. DOTTER, *Portland, Ore.*
J. RUSSELL ELKINTON, *Philadelphia, Pa.*
A. STONE FREEDBERG, *Boston, Mass.*
HARRY GOLDBLATT, *Cleveland, Ohio*
HAROLD D. GREEN, *Winston-Salem, N. C.*
DWIGHT E. HARKEN, *Boston, Mass.*
HANS H. HECHT, *Salt Lake City, Utah*
EDGAR A. HINES, JR., *Rochester, Minn.*
FRANKLIN D. JOHNSTON, *Ann Arbor, Mich.*
H. M. MARVIN, *New Haven, Conn.*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*
DAVID F. OPDYKE, *Rahway, N. J.*
GEORGE A. PERERA, *New York, N. Y.*
DAVID D. RUTSTEIN, *Boston, Mass.*
HOWARD B. SPRAGUE, *Boston, Mass.*
ISAAC STARR, *Philadelphia, Penna.*
HELEN B. TAUSSIG, *Baltimore, Md.*
GEORGE E. WAKERLIN, *Chicago, Ill.*
JAMES V. WARREN, *Durham, N. C.*
JAMES WATT, *Bethesda, Md.*
IRVING S. WRIGHT, *New York, N. Y.*

ASSOCIATE EDITORS

EDGAR V. ALLEN, *Rochester, Minn.*
SAMUEL BELLET, *Philadelphia, Pa.*
PAUL M. ZOLL, *Boston, Mass.*

PUBLICATIONS COMMITTEE OF THE SCIENTIFIC COUNCIL
AMERICAN HEART ASSOCIATION

IRVING S. WRIGHT, *Chairman*, *New York, N. Y.*
H. M. MARVIN, *Vice Chairman*, *New Haven, Conn.*

PAUL S. BARKER, *Ann Arbor, Mich.*
STANLEY E. BRADLEY, *New York, N. Y.*
J. SCOTT BUTTERWORTH, *New York, N. Y.*
IRVING B. HEXTER, *Cleveland, Ohio*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*

CHARLES D. MARPLE, *Medical Director, American Heart Association, New York, N. Y.*

HERRMAN L. BLUMGART, *Boston, Mass.*
HOWARD P. LEWIS, *Portland, Ore.*
CARL J. WIGGERS, *Cleveland, Ohio*

Interlingua Summaries by Science Service, Division de Interlingua, New York, N.Y., ALEXANDER GODE, Chief.

Circulation

JULY, 1956
VOL. XIV NO. 1

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

An Editorial on Editorials

WITH this issue it is planned to publish editorials as a regular feature. It is believed that editorials may serve useful purposes in this journal, in addition to the reports of original research and the reviews in "Clinical Progress" and "Clinical Conferences."

Editorials are chiefly expressions of opinion. Since the human intellect has infinite versatility, editorials usually display refreshing variety. The fact that this Journal is concerned with cardiovascular disease can hardly be regarded as confining. For, as our perception of the interplay between the circulation and the functions of every organ has widened, cardiology has almost ceased to be a specialty; rather, it embraces and is embraced by all of medicine. Our comprehension of the physiology and disorders of the cardiovascular system has drawn on all medical disciplines and fields of biology and science. Advances in metabolism, nutrition, electrophysics, radioisotopes, blood coagulation, bacteriology, immunology, genetics, physical chemistry, and biochemistry are but a few disciplines that may be cited. For a clinician or an investigator to be conversant with the main trends and the stage of evolution of knowledge, even in fields adjacent to his primary interest, is not only difficult but indeed often impossible.

Moreover, the clinician is confronted by the even more urgent and at times agonizing decision as to whether knowledge has reached the stage where it may justifiably and safely be applied to the improvement of diagnosis and treatment of his patient. Editorials are not oracular pronouncements that can provide complete answers to all these diverse problems; they may be of assistance, however, when written by an authority in a given subject.

In cardiology, as in medicine in general, knowledge regarding certain phenomena, such as atherosclerosis, may be considerable but incomplete. To survey the territory and delineate the areas that are already established and those that are wholly or incompletely explored may greatly hasten progress. By clearly defining the gaps in our knowledge, further speculation, clinical observations, and productive research are stimulated.

Editorial writers for a scientific journal should be selected with the most scrupulous care. They should be as wise as can be expected of man; they should be broad in their outlook; their integrity should be of the highest; and they should be possessed of detailed knowledge of the subject about which they write. They are entrusted with a grave responsibility, that of guiding and influencing the thoughts of those less familiar with the field; this may have a long-range effect. In medicine it often indirectly affects the lives of others. The writer should attempt to present his subject without bias. Unhappily, the perfect editor who would fulfill all these qualifications does not exist in this human world. Complete freedom from bias is probably not within the power of man. The editor's experience up to the moment of expression of an opinion focuses as if through a lens to produce an image. What comes forth may be true or false, or arise from that shadowy area where confusion and half-truths lie. This presents special difficulties in a field such as medicine. Emotions play a part that cannot be ignored. We have seen leaders of medicine influenced by one or two good or bad experiences with a drug to such an extent that strong evidence, which is later available in one direction or the other, is discounted. One can say that this is not science, but their opinions expressed

publicly through teaching or editorials may confuse the issue for long periods. In some controversial areas asking for a judgment regarding the recent findings of other workers may be like asking for an impartial history of the Civil War written from the Southern viewpoint.

It is not uncommon for a smoothly and even convincingly written article to represent in fact a facade for a shabby edifice. To determine value the buyer must examine what lies behind the final product. Editorial errors in the evaluation of reports may be quite apparent to those expert in a field, but they may also influence and confuse practitioners and students who tend to accept an editorial as an authoritative stamp of approval. Even those well acquainted with a field and its workers, and possessing familiarity with its possible pitfalls as a result of personal experience, may err in their conclusions; but it is reasonable to assume that such writers are less likely to err in this manner. Under no circumstances, however, should editors be regarded as "sacred cows" whose prophecies or opinions are above attack. In the final analysis what they present are merely the conclusions of individuals and should be regarded as such.

A custom, which fortunately appears to be on its way out, is that of allowing the editors to cast their darts about from behind the cloak of anonymity. Editorials should be signed, indicating that the writer stands foursquare behind his statements.

Perhaps the greatest services that an editorial writer can perform are to direct attention to the most promising of new studies or areas of investigation, and to question accepted theories, the bases of which seem insecure. His own knowledge of the field should help him to cull the grain. His challenge is to stimulate the reader to study the original reports critically and with fair scepticism regarding the thoroughness of case or experimental data, the care with which controls are planned, the validity of the statistical analysis (frequently the weakest component of a medical paper), and the background and character of the authors.

It is the editor's constant hope that he will stir some latent thought process, will initiate a chain reaction, will activate a young mind to pursue an original approach toward a scientific problem, or will stimulate a physician to learn more about a disease or an entire discipline. Research advances in the field of circulation are very exciting today. The horizons are limitless. The paths are new and varied. They are, however, often confusing, and it requires special skills to cut through in the right directions.

It will be an objective of the writers of this series to apply their experience and knowledge in pointing toward the most promising of these trail-blazing efforts.

IRVING S. WRIGHT, *Chairman, Publications Committee*

HERRMAN L. BLUMGART, *Editor-in-Chief*

The Nurture of Cardiologists

Presidential Address*

By IRVINE H. PAGE, M.D.

THE American Heart Association has become, I believe, a symbol of the hopes, fears, aspirations, and beliefs of both practitioners and the more specialized cardiologists. But it has grown to be much more than that: it represents something unique—an amalgamation of laymen, physicians, and scientists that has no parallel with which I am familiar. In this fusion lies the strength of this organization. The mutual education of physician and layman is truly heart warming. This process of fusion has led to the collecting of what I have so often referred to as the "intelligent dollar."

The education of the thousand upon thousand of volunteers who do the hard work of collecting dollars is another phenomenon of great importance. A reservoir of knowledge is thus being created on which all community services and health plans can be based. A mother who knows that streptococcus sore throat may lead to rheumatic fever is an asset not only to her own family but ultimately to the nation as well. A family who understands the true meaning of a heart attack and copes with it intelligently is a blessing for the victim. Education can abolish fear and substitute understanding.

I suppose there are few medical fields changing more rapidly than cardiology. The realization that cardiovascular diseases numerically outstrip all others by manyfold has proved a strong stimulant. A lugubrious recommendation, indeed, but one we must heed. Much that is good has been done, but we must ask ourselves whether we have matured enough to admit the bad along with the good. I think we have. I have no intention of acting the professional curmudgeon. What I have to say about the deficiencies of cardiologists is only by way of some clues to their remedy; and in so doing I hope not to fall under Dr. Hutchinson's castigation of the vegetarian and his diet which, "while harmless tends to fill a man with wind and selfrighteousness"; much like the man who has recently given up smoking.

The past 20 years have seen the unfolding of the first act of the great drama of the fight against heart disease. The objectives have been clearly defined, which is the beginning of all knowledge. Much of both practical and theoretic value has been accomplished. This is so obvious I need not even be specific. Not only have many discoveries been made, but the secret is being found of how to translate them into immediate use at the bedside. In my opinion, never before have we had such a large number of highly trained cardiologists. I cannot help believing that this greatly accelerated program of training was in no small part due to the activities of the American Heart Association and the extramural program of the National Heart Institute of the U. S. Public Health Service. All this gives us no right to be self satisfied. Rather we must seek to improve our actions in the future, for in seeing our own faults we can correct them.

At the moment there are but 10 areas I think could be improved in our cardiovascular past imperfect.

1. *Attending to the Causes of Disease Rather than their Results.* Coronary heart attacks have been treated for years and have been very accurately described, but we still do not know why they happen. Arteriosclerosis which underlies the heart attack has no doubt been discussed for 5000 years, but only in the past twenty have we tried seriously to uncover its

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio

* October 23, 1955, American Heart Association, New Orleans, La.

cause. Too long a latent period, I say. We are to some extent mired down in the stage of detection and measurement—the phonocardiograph, the ballistocardiograph—and rather early in that stage to boot, because even these imposing instruments leave much to be desired. We still have no means of detecting arteriosclerosis in the coronary vessels except by examining the heart after death. On the credit side, there is indisputable evidence that descriptive cardiology is rapidly being replaced by a penetrating search for causes. The corner has been turned, thanks to the intelligence of the research workers, the practitioners and the current high-level thinking of our lay associates. Let us, then, create an intellectual climate in which the "why department" is given precedence over the department of "what."

2. *Thinking in Terms of Mechanism.* It should be evident to you that there are a few of us who still are not clear as to why or how arterial blood pressure rises to preternaturally high levels, as in hypertension, or falls to excessively low ones, as in shock. As a matter of fact, we do not even know what keeps it normal in healthy people. At least we are no longer content with the notion that blood pressure rises merely to compensate for the increased resistance to the flow of blood through the tissues, which occurs in hypertension. What we want to know is the mechanism of the increase in resistance of the arteries and arterioles to the flow of blood. Along the same line, it now seems as unlikely as it seemed likely 50 years ago, that the blood vessels become hardened with arteriosclerosis merely to protect a weakened wall from blowing out. Let us hope that cardiologists of the future will not only observe cardiovascular disease at the bedside, but will emphasize the great importance of finding out what disturbance in mechanism has occurred which led to manifestations of the disease.

Mechanism of disease must be added to cause, if disease is to be understood in its entirety. This will require more than money and the materials of science; it will require, in great measure, that inexplicable attribute of man called curiosity; curiosity to understand the riddle of himself. Some of us may not be able to share in this quest as fully as others more gifted; but at least we can come more to appreciate the power and beauty, not just the utility, of the human intellect.

3. *Reintegration of Heart, Kidneys, and Brain —in short, the Cardiovascular System.* Without this coordination, we have "cardiologists," "angiologists," "cardiac surgeons," "peripheral vascular men," and, of late, the more glorious "nephrologists." It is our own fault. As long as we magnify one portion of the circulation at the expense of another, this sort of thing happens. Unfortunately, there seems no term to cover the entire circulation. We seem stuck with the appellation, "cardiologist," but in our own thinking, let us make a fresh start. For just a moment consider the heart as only a "specialized nubbin" on the whole vascular tree; let us reintegrate the heart and blood vessels back into the unified system that it really is. As Jan Smuts thought, the whole might turn out to be greater than its parts. This view has, I think, been reflected in the organization of the American Heart Association. We have only to put these principles more actively into practice.

4. *Consideration of Metabolic Substances such as Salt in Terms of Total Turnover.* You all remember the shock and surprise that followed the announcement by my old friend Rudolph Schoenheimer of the concept of a constant building and tearing down and rebuilding of the body. This dynamic view, derived from isotope studies shows, I think, why very small amounts of a substance, such as a teaspoon a day of ordinary table salt (sodium chloride) can get you into trouble. Burch found that about 32 per cent of all the sodium diffuses out of the blood every minute. This turns out to amount to about 50 pounds of sodium chloride crossing the walls of the blood vessels per day. How easy it would be for some of it to get out of the proper metabolic channels and pile up in the tissues to elicit edema, and worse, to aggravate hypertension. Likewise, the kidneys filter something like 195 liters of water a day but excrete only a liter and a half. That would be quite a difference if 193½ liters were not reabsorbed. Reabsorption is a little less complete

in the very young; but if the child did not have a fairly retentive kidney epithelium, think what a mother would have to cope with, and consider the mountains of diapers.

I sometimes wonder if the constant metabolic turnover in the brain does not account for some of my own troubles. Just how the brain builds, tears down, and rebuilds itself without loss, or even with it, utterly baffles me. I can only say that it probably explains many of the weaknesses that appear as we get older, for who could expect not to have lost some of the pieces during so many rebuildings. To have a "screw loose," or have one button missing, need cause no surprise under this dynamic concept. It is a wonder it does not occur more often—or does it?

5. *Thinking in Terms of Equilibrium or States of Balance.* Democrates recognized 2500 years ago that "all things are in a state of flux." An excellent example of an equilibrium is the state of balance between the amount of blood put out by the heart and the resistance to its flow in the blood vessels. In short, to keep things on an even keel, the body continuously alters its regulatory functions in relation to each other. When one changes, others must change in such a way as to keep constant the function being regulated. The maintenance of constancy of the internal environment in a hostile world has caused the organism to develop an elaborate control system. In complexity, this makes the "servomechanical feed back" look pre-Harveian.

There are, for example, at least 8 factors concerned with maintaining blood pressure at a set level, but there is no steady degree of participation of each of these factors. No, it is a shifting participation depending on the needs of a particular tissue for blood at a special time.

The problem of the control of blood pressure differs in different animals. For example, as Goetz has shown, the giraffe has a blood pressure of 300 mm. Hg without at the same time suffering from hypertensive disease. If your head were 17 feet above your heart and you could not elicit more than the usual 120 mm. Hg pressure, there would certainly be little going on in your brain for lack of blood. You see, being born a giraffe introduces problems of blood pressure regulation that only giraffes have so far solved to their own satisfaction. Not only are the controls of blood pressure set so as to provide a higher pressure but even the blood vessels that have to withstand these high pressures are especially constructed, at least as compared with human beings. Blood pressure thus becomes only one component of a total system which subserves the need of the body for blood. It can only be put in proper perspective when its relationship to the other components of the cardiovascular system are understood. These relationships are best understood when translated into terms of equilibria.

I like to think the time is not far off when we can construct diagrams in which these interrelationships can be both visualized and dramatized. These could be the equivalent in cardiovascular physiology of Willard Gibbs' "phase rule," described by Muriel Rukeyser in her biography of him, or of the nomograms used by Laurence Henderson to vivify the complex interrelationships of the components of blood. The data of cardiovascular physiology and chemistry are probably still too crude for these types of representation; nonetheless, I suggest them as important ways of thinking in our field for the future.

Knowledge built on a structure of equilibrated interrelationships would do much to avoid current confusion bred of thinking in terms of single, unrelated phenomena.

6. *The Integration of Discoveries in Basic Science into Clinical Cardiology.* This I have constantly urged, as many of you know. I shall dismiss it, for once in my life, with the brief statement that the American Heart Association spends at least half its research money for basic science. If this is sound policy then let us make every possible effort to integrate the results of this work in fundamental sciences with clinical cardiology. I think our current plans and policies will almost inevitably lead to this integration, but it requires more than usual effort, tolerance, and understanding on both the basic and clinical sides of the fence, as many of us are finding out.

The educational programs of the American Heart Association are performing yeoman service in putting into the hands of practicing physicians the latest practical results of basic research, and much of the theoretic as well. It is an altogether heartening thing to watch. The rapid growth of understanding and appreciation of the basic sciences by our physician members provides the underpinnings for the research program the Association now sponsors. The idea that the practicing physician has no time for, or interest in, basic science, is utter nonsense, and this opinion I have formed from a good many years of traveling around the country among them. A structural formula no longer frightens even a surgeon, and the von Bezold reflex is no longer a bad word.

Integration particularly needs the help and inspiration of the basic scientists. To date, most of them have been negligent in this regard. They must show more leadership than in the past and more interest in creating the kind of environment in which science and the practice of medicine can flourish together. I hope the new basic science section will provide some of this leadership—what one of my patients called a "shot in the buttress," in referring to certain aspects of his own medical problems.

I hope also that the clinical syndrome I shall refer to as Ph.D.-itis will correspondingly become less prevalent. With the influx of those with Ph.D.'s instead of M.D.'s into hospitals, or any institution where there is a preponderance of clinicians, there has been a definite increase in the number afflicted, and is characterized chiefly by wholesale condemnation of all physicians, just because they are physicians. This form of overcompensation is a more serious disease than we had formerly thought.

A human being who has no desire to seem in some way important is probably not worth his keep. The Ph.D. must be given his importance in an atmosphere surcharged with that of the clinician, and that is not an easy thing to do. But, as cardiologists, if we are to attract and keep scientists of great competence, then most careful planning of the environment is essential to provide the necessary ego satisfaction. The best cure of the disease is never to let it start.

And lastly, scientists have their own responsibility for help in educating the public in understanding the need for fundamental or basic research. The idea is not difficult for laymen to understand if clearly presented and, furthermore, they can become deeply interested. It is the furtherance of this kind of interest that leads to the concept of "intelligent dollars." More than that, it leads to the emotional oneness of both scientist and layman in this great adventure of research that has come to be the core of most great economic and social movements. The days seem to be largely over when scientists had no part in the building or control of the environment in which they lived and worked. If they would now have a hand in its shaping, they must take some of the responsibility for providing the means by which it can be shaped.

7. *The Training of Enough Good and Wise Medical Politicians, or "Statesmen."* Let us face the fact that, for better or worse, physicians and scientists are squarely in the middle of politics, not only their own, but the government's as well. To me, all this means is that the world has become complex, large sums of money are involved, and the impact of people on one another has greatly increased in intensity. The social temperature has risen, and the Brownian movement increased. The positive chemotaxis of the dollar on scientists is an observation I made 30 years ago. The need for skillful politicians is thus greatly augmented, just as it is for an informed electorate. I mean by politician just what the dictionary says, "one skilled in the science and art of government," of whatever sort. The term should have no derogatory connotation. In short, the American Heart Association, a 13-million-dollar organization, must be managed in all aspects—professional, social, and financial—by people of experience; the same applies to most phases of medical practice and research as well. The time will come, I hope, when far more young cardiologists and investigators will be given political jobs in our own societies, training them early for bigger ones as their experience grows.

The American Heart Association has a great responsibility in the training of a vigorous and

healthy group of young statesmen charged with shaping a productive future for cardiology. A cursory look shows that the Association is recognizing its responsibility. I might add that the recruitment and training of enough good scientists is an even more pressing and immediate problem, but one that would require more than passing discussion. The cardiovascular research field is very short of good workers. I wonder if the secondary schools and the colleges could be enlisted to help us find the youngsters who might make their careers in cardiovascular research if they only knew about it?

8. *The Need For the Production of Useful Remedies and Preventatives at Reasonable Prices.* In our preoccupation with ourselves, we sometimes forget that the care of patients is profoundly influenced by forces other than those from the physician. Among the most important of these is the pharmaceutical and chemical industries, and yet little has been done to find either the philosophical or practical aspects of a working relationship. I think this a pity for the physicians and the industries, but it may be a tragedy for the patient. There are many aspects of these relationships I would like to discuss but this is not the place. I shall single out just an illustration or two. Parts of industry still need to be persuaded that solution of basic problems is a necessary prelude to a healthy economy in drugs. This is surprising when you see how effectively other parts of the industry have operated.

The integration of the pharmaceutical industry with research and the practice of cardiology requires much more thought than it has been given. In fact, I doubt that it has been given much thought at all. Certainly no policies have been established that will provide precedents on which to operate. I would hope that some day a more enlightened relationship could be established by the American Heart Association in cooperation with the leaders of the industry, which would provide some ideals for which to strive. Currently, for example, we are mired in exaggerated claims for competitive products that differ only insignificantly; claims of increased potency, which about doubles the price of the product for the privilege of taking a few milligrams less of the drug, and mixtures of drugs in one pill that preclude any possibility of regulating dosage of the separate constituents. These only illustrate the problems.

Some of the advertising is excellent and well worth the physician's time; much of it is subtly mediocre and designed alone to sell, rather than to inform. It is the kind in which references to the literature are either to obscure journals, to unpublished observations, or limited strictly to adulatory articles. Then there is the downright ridiculous, and often much more amusing, consumer type, such as "... includes in its formula the *whole* egg, which acts on the skin like hormones, but which are not ... it effects lovely dewy freshness ... and an effective blandishment against wrinkles."

We have lost much of our critical faculty when we do not object actively to the abuse of our patients pocketbooks by the peddling of such things as mixtures of vitamins, minerals, hormones, lipotropes, trace minerals, and what not, which are said to prevent the ravages of old age, cardiovascular disease, and make retirement one happy day after another on the beach throwing plastic medicine balls, swinging in a hammock with a greying, attractive blond and benignly watching others do the work of the world.

I would like to leave the notion that the intellectual relations of cardiologists and the pharmaceutical industry could stand improving.

9. *The Avoidance of Fear and Cant.* There is always danger in our enthusiasm to promote cardiology that we employ the emotion, fear, for our own selfish purposes. This is often a subtle technic and may be quite unconscious; worst of all, it usually brings the desired result, whether it be submission to the diets we think best for the patient or increased financial contributions. While it is altogether desirable to educate the public, it is not all right to have our way by frightening them into submission.

Let me give you an example of what I mean. We say that coronary heart disease is the American man's greatest killer. We could then suggest that every male in the United States have his heart examined and an electrocardiogram taken every 6 months with the object

presumably of preventing heart disease or detecting it, if present, and treating it. The only trouble is, as you all know, we do not know how to detect latent coronary disease, we do not know how to prevent it, and we know little enough of how to treat it. Let us then adhere, as rigidly as we can, to our current policy of improving understanding of heart disease within the framework of the phenomena of nature. We must teach how to live with heart disease, not fear. The contribution of the "intelligent" dollar must remain for the primary purpose of furthering research in all aspects of heart disease. Our contributors should be told this. In the long run, we may not collect as many dollars, but we will have resolved some of the problems of heart disease without spreading unhappiness. We shall avoid dissatisfaction if we do not promise what we cannot currently give. A recent example of a promise kept is the rheumatic fever control program. I believe education will do the trick without mentally transforming every sore throat into the fear of a killing heart disease.

There is another aspect of the cardiologist's public relations which, I think, requires watching. In the past few years, more and more we have been against an increasing number of things the public is in the habit of enjoying. They like to overeat, smoke, drink, live tensely, and not take exercise. Some of us are inclined to frown on most of these activities to a greater or lesser extent. At any rate, the number of suggested "can'ts" has become formidable. I am not going to add another by telling you what you "can't" tell the public, but I am going to suggest either (1) you don't tell the public they can't do so and so until you are sure of your ground or (2) try the "can't" yourself before you recommend it to others. First, stop smoking, then try a saucer of unsalted rice and some fruit juice for breakfast, lunch, and supper (no cocktails, mind) for a week or so and see how much longer you care to live. If we must forbid, let us try to ameliorate the blow with understanding and, more importantly, with moderation if at all possible.

10. *The Cultured Medical Mind.* I believe that the practicing cardiologist has come a long way in developing genuine interest in more than the mere tools of his trade and their application—the mechanics of cardiology if you will. I think if you compare the content of the programs of the American Heart Association today with those even 10 years ago you will see that it is not a change in the tools alone, but rather a change in philosophy. This I rate as altogether good. A more mature and encompassing understanding of disease can hardly fail to follow.

But, if we are to keep the field of cardiology flexible, progressive, and intellectually mature, we must not fear to criticize ourselves. Only in this way can the American Heart Association build the environment in which future cardiologists will be properly nurtured. I personally think we are well on our way, and I would have few qualms for the future.

One more note I feel impelled to add. Never lose sight of the fact that the world today, as always, hungers for ideals; ideals to counter the curse of our century—that cruel, destructive, unrealistic materialism, seeking sanction under the guise of "practicality." As physicians, we must heed and nurture the spirit of man which alone is capable of compassion, sacrifice, love, inspiration, hope, and conscience. Only man contemplates his own nature and the nature of the universe, and from them discerns a higher nature than either.

If this be so, ladies and gentlemen, the indissoluble linkage of mind and heart must turn the narrow specialists back to contemplation of the whole.

Results of Valvulotomy for Valvular Pulmonary Stenosis with Intact Ventricular Septum

Analysis of Sixty-Nine Patients

By Don M. Hosier, M.D., John L. Pitts, M.D., and Helen B. Taussig, M.D.

The analysis deals primarily with follow-up studies of patients who have had a valvulotomy for valvular pulmonic stenosis with an intact ventricular septum. In addition to observations on the subjective improvement, hemograms, and arterial oxygen saturation, the cardiac findings have been analyzed in detail. The changes in the size of the heart have been studied in relation to the growth of the patient and, wherever possible, these changes have been correlated with the postoperative right ventricular pressure. It was found that cardiac enlargement came to an end when the right ventricular pressure fell below 100 mm. Hg.

EIGHTY-SIX patients with valvular pulmonary stenosis and an intact ventricular septum had a valvulotomy performed by Dr. Alfred Blalock or one of his associates at the Johns Hopkins Hospital between November 1949 and November 1953. There have been 7 deaths in this series of 86 patients. It is of interest and of possible significance that all patients who died were cyanotic. One death occurred on the third postoperative day from an unsuspected brain abscess. Two of the other deaths occurred in patients in whom an anastomosis was performed because of the erroneous diagnosis of tetralogy of Fallot; both died at the time of the pulmonary valvulotomy. Two other patients who had had an anastomosis for tetralogy of Fallot survived a pulmonary valvulotomy; these 2 patients, however, are not included in this analysis of the operative results because the anastomotic procedure grossly altered their clinical findings. In addition, there are 8 patients in whom follow-up studies have not been adequate. Hence, this analysis of the operative results deals with the 69 patients upon whom we have postoperative follow-up studies for periods varying from 3 months to 4 years.

From the Department of Pediatrics of Johns Hopkins University and the Harriet Lane Home, Cardiac Clinic Johns Hopkins Hospital, Baltimore, Md.

Preliminary report presented at the Second World Congress of Cardiology Washington, D. C., September 1954.

Subjects

Of the 69 patients, 40 were female and 29 male. The age at the time of operation ranged from 5 months to 27 years. There were 2 patients under 1 year of age; 4 between 1 and 2 years; 14 between 2 and 6 years; 24 between 6 and 12 years; 14 between 12 and 18 years; and 11 patients over 18 years of age.

Complete information on all aspects of the postoperative results was not obtained on every patient but, whenever possible, we have compared the preoperative and postoperative exercise tolerance, hemograms, and arterial saturations, and have studied the changes in the size of the heart. Finally, the changes in the size of the heart have been correlated with changes at cardiac catheterization.

Seven patients have been followed for 3 to 6 months postoperatively; 14 for 7 months to 1 year; 15 for 1 to 2 years; 11 for 2 to 3 years; and 22 for more than 3 years.

Results

Subjective Improvement. The subjective improvement in exercise tolerance following pulmonary valvulotomy has been repeatedly reported. Even though it is probably the least reliable criterion for successful operation, a careful evaluation of this feature is of some merit.

Sixty-eight of the 69 patients in this series have shown definite evidence of subjective im-

TABLE 1.—*Results of Preoperative and Postoperative Cardiac Catheterization in Seventeen Patients*

	Preoperative				Postoperative			
Pt. No.	Age (yr.)	Right ventricular pressure	Pulmonary artery pressure	Arterial oxygen sat. (%)	Time post op. (mo.)	Right ventricular pressure	Pulmonary artery pressure	Arterial oxygen sat. (%)
1	5	96/0	N.E.§	62.0	6	58/0	24/17	86.2
2	13	143/0	22/9	95.6	11	80/0	N.E.	96.0
3	14	122/30	N.E.	93.5	7	100/3	N.E.	89.5
4	4	165/36	N.E.	92.3	6	135/34	N.E.	91.7
5	13	223/13	14/6	93.5	13	148/0	14/10	94.5
6	7	166/26	16 mean	83.6	12	70/0	20/9	99.0
7*	1¼	84/60	N.E.	71.0	11	37/14	20/13	92.4
8†	11	126/40	N.E.	72.7	1	92/34	N.E.	73.8
9	14	160/3	12/10	60.5	7	88/2	26/11	94.3
10‡	20	66/12	N.E.	94.5	8	61/8	18/11	100.0
11	9	178/0/13	12 mean	77.5	2½	90/0/12	N.E.	88.5
12	8	200/20	N.E.	—	25	65/0/8	32/8	—
13	13	145/3	24/9	96.0	5	111/5	35/13	93.2
14	12	213/0	13/4	79.6	11	55/3	26/8	89.0
15	20	117/12	24/12	100.0	11	55/5	24/12	100.0
16	7	144/26	16/11	79.6	24	40/2	18/8	100.0
17	19	130/2	25/8	94.1	21	38/0	16/6	98.2

* Dampened pressure.

† Patient believed to have an anomaly of pulmonary venous return.

‡ Patient in heart failure at time of catheterization.

§ N.E.—Not entered.

provement. Indeed, only 1 patient (B.I., #8 in table 1) has failed to show improvement; this patient had a 2 to 3 volume per cent step-up in the right atrium prior to and following operation, and it is believed that she has an anomaly of the pulmonary venous return in addition to pulmonary stenosis.

Prior to surgery, 19 patients, who were unable to walk 1 level city block without stopping to rest, were considered markedly incapacitated. There were 35 patients who became fatigued only after walking more than 1 block; these patients were classified as moderately incapacitated. Ten patients complained of shortness of breath on running or climbing stairs; hence, they were classified as slightly incapacitated. The remaining 5 patients were less than 2 years of age at the time of surgery, and consequently their exercise tolerance could not be evaluated. These 5 patients, however, showed excessive dyspnea on moderate exertion.

Postoperatively, 52 patients now have no limitation of activity, i.e., they are capable of participating in sports although competitive athletics are not recommended. This group includes the 5 patients whose exercise tolerance could not be evaluated prior to surgery. All 5 have now been followed for more than 1 year after operation and are considered to be leading normal, active lives. There are 15 patients who show slight limitation of activity, all of whom were incapacitated prior to operation. Two of these 15 patients have shown no demonstrable change in exercise tolerance. Both were classified as being slightly incapacitated prior to surgery, and neither is capable, at the present time, of participating in the same activities as their coevals without experiencing undue dyspnea. There remain 2 patients whose postoperative exercise tolerance cannot be evaluated, because they have been followed for only 3 months and have not yet been allowed unrestricted activity.

Cyanosis. Cyanosis, as is well known, may or may not be present in patients with valvular pulmonary stenosis with an intact ventricular septum. Prior to operation, 40 patients showed cyanosis at rest. There were 4 additional patients who were acyanotic at rest, but manifested minimal cyanosis during strenuous activity. It is worthy of note that there were 3 patients in this group who were cyanotic during early infancy in whom the cyanosis decreased as they grew older.

Postoperatively, cyanosis has been observed in only 7 patients. Three of the 7 are cyanotic at rest and 3 show minimal cyanosis with activity. Only one patient (B.I.)* has remained markedly cyanotic following valvulotomy.

Blood Cell Counts. The red blood cell counts varied with the presence or absence of cyanosis. The red blood cell counts prior to operation ranged from 3.8 million/cu. mm. to 10 million/cu. mm. There were 24 patients with counts below 5.5 million/cu. mm.; 23 patients between 5.5 and 6.5 million/cu. mm.; and 22 patients with counts over 6.5 million/cu. mm. Eight of the 69 patients had counts above 8.5 million/cu. mm. At the time of their last postoperative examination, 54 of the 69 patients had red blood cell counts below 5.5 million/cu. mm.; 14 had counts between 5.5 and 6.5 million/cu. mm. The only patient whose red blood cell count remained over 6.5 million/cu. mm. is the cyanotic

* This is the patient who is thought to have an anomaly of the pulmonary venous return.

patient (B.I.) previously referred to, who was unimproved by operation. This patient's red blood cell count remained at 7.23 million/cu. mm.

Oxygen Saturation. Oxygen saturation of the arterial blood was determined both preoperatively and postoperatively in only 26 patients. Seven had a preoperative arterial oxygen saturation above 90 per cent and showed no significant change after operation. The other 19 patients had preoperative arterial oxygen saturations that ranged from 73 to 90 per cent (fig. 1). In 16 of these patients, the postoperative arterial oxygen saturation was above 90 per cent, while in only 3 patients the arterial oxygen saturation remained below 90 per cent. In 2 of these 3 patients, the saturations were 86 and 89 per cent and, in the remaining (B.I.), the postoperative arterial saturation remained unchanged.

Heart Murmur. The cardiac findings were studied in great detail. The auscultatory findings preoperatively were fairly uniform. A harsh blowing systolic murmur along the left sternal border that was maximal in the second and third left interspace was the rule. The murmur radiated upward toward the left clavicle. In only 1 patient was the murmur maximal to the right of the sternum; this patient was thought to have an associated anomaly, possibly subaortic stenosis. A systolic thrill was palpable along the left sternal border in all but 9 patients. The second heart sound in the pulmonic area was considered to be diminished in all but 3 patients. In these 3 patients, the second sound in the pulmonic area was thought to be of slightly greater intensity than normal. Reduplication of the pulmonic second sound was never heard in this series of patients. A gallop rhythm was heard at the apex in 8 instances.

The postoperative change in the murmur was somewhat difficult to evaluate as, in many instances, the same physician did not examine the patient on both occasions. The murmur, however, was thought to be less intense in 24 instances. Furthermore, in 14 patients, a systolic thrill, which had been present preoperatively, was no longer palpable following the valvulotomy. The second sound in the pulmonic area was considered to be reduplicated in 4 patients, and of greater intensity than preoperatively in 5 other patients. Postoperatively, a short soft diastolic murmur was heard in the pulmonic area in 15 patients. The murmur was thought to represent some degree of pulmonary insufficiency. Blount[3] and his associates have recently reported the results of open valvuloplasty of the pulmonic valve and, in 4 of the 5 patients subjected to this procedure, a diastolic murmur was heard along the left sternal border. In our series, the development of pulmonary insufficiency has not apparently altered the postoperative course of these patients.

Liver. Engorgement of the liver was noted in 24 patients prior to valvulotomy and, in 20 of these patients, pulsations at the margin of the liver were detected. Of these 20 patients, 13 were cyanotic and 7 were acyanotic. Pulsations ceased almost immediately following the valvulotomy and, in every instance, the liver decreased in size.

Edema. Edema was present in 8 patients prior to valvulotomy and was not demonstrable in any patient on follow-up examinations.

Electrocardiogram. The electrocardiographic changes following pulmonary valvulotomy have been carefully analyzed by Landtman[4] and, therefore, are not included in this report. Landtman showed that, following surgery,

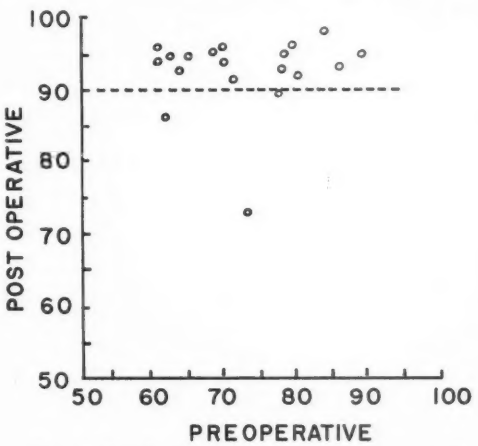


FIG. 1. Level of preoperative and postoperative arterial oxygen saturation found in 19 patients with pulmonary valvulotomy.

there was a positive correlation between the extent of the changes in the electrocardiogram and of the fall in the right ventricular systolic pressure. The most significant changes, indicative of improvement, occurred in those patients whose right ventricular systolic pressure fell to below 100 mm. Hg.

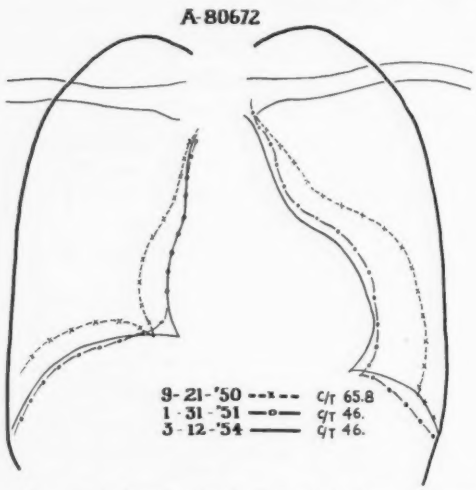


FIG. 2. A decrease in the size of the heart following pulmonary valvulotomy in an adult (patient no. 10 in table 1).

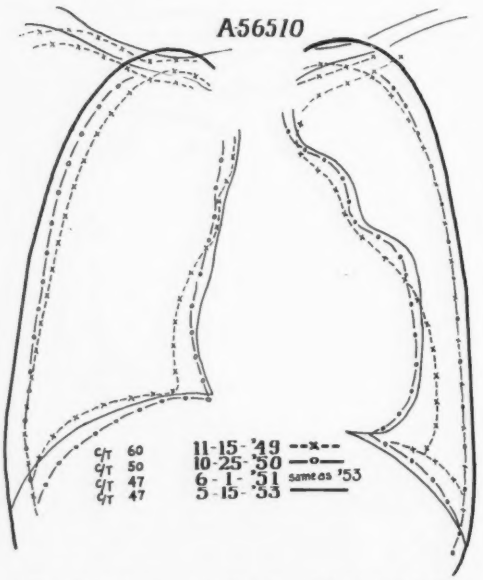


FIG. 3. A decrease in the size of the heart following valvulotomy in a 13-year-old boy. Thereafter heart and chest grew proportionately and cardiothoracic ratio remained constant (patient no. 2 in table 1).

Heart Size. Changes in the size of the heart were studied by a comparison of the preoperative and postoperative teleroentgenograms. Both the immediate changes, those that occurred within the first 3 weeks, and the late changes, those that occurred over a period of years, were studied. X-ray films taken within the first 3 weeks following valvulotomy were available for comparison with the preoperative films in 59 instances. As was to be expected, the greatest changes occurred in the patients with the largest hearts. A review of these films showed 2 distinct changes. In the group over 18 years of age, 4 of the 5 patients with marked cardiac enlargement showed a prompt decrease in the actual size of the heart. In contrast, 4 of 5 infants, 2 years of age or under, with marked cardiac enlargement, showed an increase in the size of the heart at the time of discharge from the hospital, 3 weeks after operation. The 1 exception to this phenomenon was a 16-month-old infant in whom, in the 2 months preceding operation, the cardiothoracic ratio had increased rapidly from 60 to 67 per cent. Immediately after surgery, this patient's heart showed an abrupt decrease in size; the cardiothoracic ratio dropped to 56 per cent. This change suggested that the previous rapid increase was due to dilatation.

In an analysis of the late postoperative changes, it was necessary to take into consideration the factor of growth. Therefore, the changes in the size of the heart were studied by the method previously used by Taussig and Goldenberg,[5] by the superposition of one x-ray film upon another, and by the calculation of the cardiothoracic ratio. There were 48 patients who had teleroentgenograms taken more than 1 year after valvulotomy. Eight of these patients were over 18 years of age and had attained their full growth. Four of these 8 patients showed a marked decrease in the size of the heart after valvulotomy; the cardiothoracic ratio decreased and thereafter remained unchanged (fig. 2). Of the remaining 4, 3 patients had hearts of normal size at the time of operation; they have shown no change on subsequent

examinations. Thus, there is but 1 patient in this group in whom the heart was enlarged prior to valvulotomy and has remained essentially unchanged in size. This patient had a marked scoliosis that rendered accurate determination of the size of the heart difficult.

There were 40 patients under 18 years of age. The analysis of the changes in the size of the heart in this younger age group showed several distinct trends. The first, and probably most favorable result, is illustrated in figure 3. After valvulotomy, the size of the heart decreased to within normal limits and thereafter the heart and chest grew together; thus the cardiothoracic ratio decreased and thereafter remained constant. There were 6 patients who showed this type of change.

In 13 instances, the heart decreased in size but remained enlarged, as shown in figure 4. In such cases, over a period of 2 or 3 years, the heart remained constant in size and the chest has grown with the child. Therefore, the cardiothoracic ratio continued to fall until the heart came to be within the limits of normality. We regard this to be a favorable sequence of events.

In 13 patients, the changes were less favorable. In these patients, the heart remained the same size or decreased slightly in size during the first 6 months after operation; thereafter, it continued to grow with the chest. In such instances, although the cardiothoracic ratio remained constant, the heart remained enlarged (fig. 5). The lack of progressive cardiac enlargement indicates an improvement, but it is not a satisfactory result.

Finally, in this group of 40 patients, there were 8 in whom the heart was normal in size at the time of operation and has remained normal in size on subsequent postoperative examinations (fig. 6). These patients were operated upon because of dyspnea on exertion, cyanosis, or high right ventricular pressure; although the right ventricular pressure was reduced, there was no appreciable change in the size of the heart. Obviously, such patients have a constant cardiothoracic ratio.

At present, 3 children appear to show evidence of progressive cardiac enlargement. Each of these children showed a decrease in the size of the heart after valvulotomy; nevertheless, the heart remained enlarged. The cardiothoracic ratio, however, is again increasing. Needless to say, such patients must

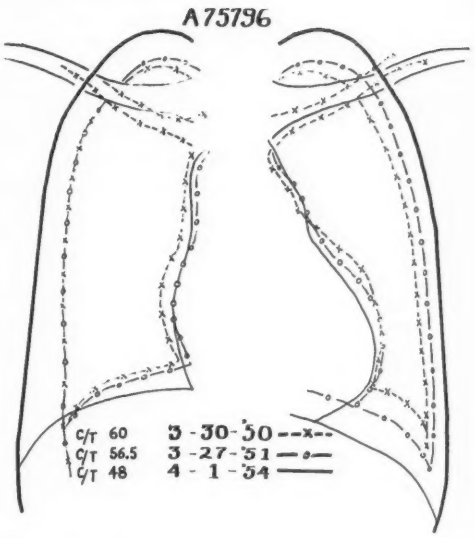


FIG. 4. A slight decrease in the size of the heart following valvulotomy with a subsequent fall in the cardiothoracic ratio due to growth of the chest without proportional increase in size of the heart.

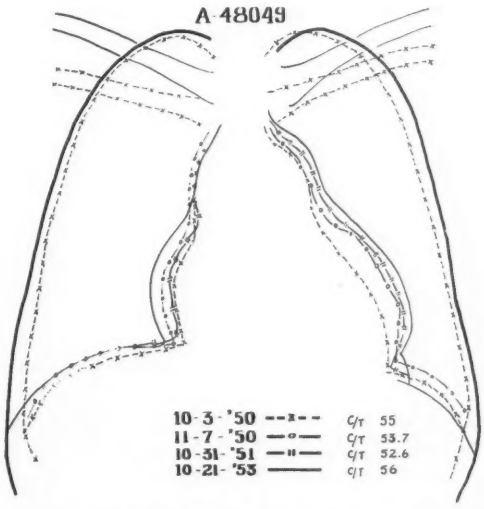


FIG. 5. The heart is enlarged but cardiothoracic ratio has remained constant following valvulotomy (patient no. 13, table 1).

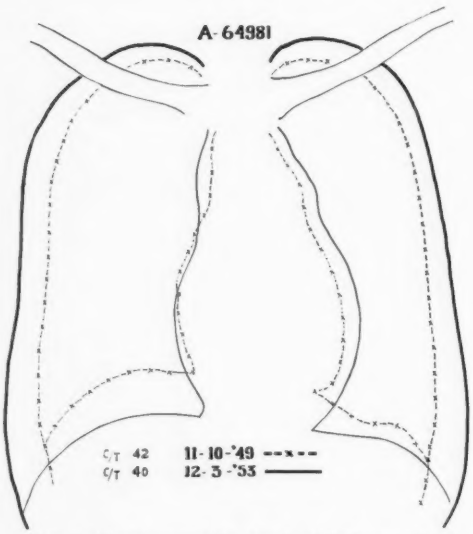


FIG. 6. Heart normal in size both before and after valvulotomy (patient no. 3 in table 1).

be kept under close observation and may require further surgery.*

The comparison of pulmonary vascularity, as visualized in the x-ray films, showed no significant change. In 9 patients, there appeared to be an increase in the size of the main pulmonary artery after the valvulotomy. In 7 of these 9 patients, it was believed that the apparent increase was in reality due to a decrease in the size of the right ventricular outflow tract.

Cardiac Catheterization. Cardiac catheterization was not a routine procedure either before or after operation. Although 48 patients had a cardiac catheterization prior to surgery, only 17 patients have had both a preoperative and postoperative cardiac catheterization. Furthermore, as is shown in table 1, cardiac catheterizations were performed at varying times after operation; 1 as early as 1 month, and 3 approximately 2 years following surgery.† It is of interest that in 2 of the 3 patients in this series (nos. 16, 17), who were catheterized approximately 2 years after surgery, the right ventricular pressure has fallen to nearly normal levels. In 4 instances, the right ventricular pressure remained over 100 mm. Hg and in one it was 90 mm. Hg. In this group the longest time interval was 13 months. Whether the right ventricular pressure continues to fall or ever returns to normal limits must await further investigation. In this connection, it is worthy of note that Soulie and his associates[6] found the most significant drop to occur in those individuals whose initial right ventricular systolic pressure was above 150 mm. Hg. These authors also concluded, from physiologic data obtained on patients who had 2 postoperative cardiac catheterizations, that the greatest fall in pressure occurred in the immediate postoperative period. We have no information on this point, as none of the patients in this series have had a second postoperative catheterization.

The correlation of the right ventricular pressure and the change in the size of the heart is of interest. Our observations indicate that the size of the heart is not solely determined by the height of the right ventricular pressure. The degree of hypertrophy, if concentric in type, may be considerable without demonstrable evidence of cardiac enlargement by x-ray or fluoroscopic examination. The compensation of the patient is also a significant factor in determination of right ventricular pressure. For example, patient no. 10 was in severe cardiac failure preoperatively with marked hepatomegaly and pedal edema at the time of her first cardiac catheterization; her right ventricular pressure was only 66/12 mm. Hg. Eight months after valvulotomy, the pressure was essentially the same, but the heart had decreased from a cardiothoracic ratio of 66 per cent to 45 per cent (fig. 2), and there was no clinical evidence of cardiac decompensation.

As was to be expected, in those individuals in whom there was no cardiac enlargement, a decrease in right ventricular pressure did not change the size of the heart. In those patients with cardiac enlargement, the decrease in the size of the heart, after valvulotomy, was not related to the magnitude of fall in pressure, but to the level to which the pressure fell.

* One patient has subsequently shown a decrease in the size of the heart.

† We are indebted to Dr. R. J. Bing, Dr. H. T. Bahnson, and their associates for these studies.

Furthermore, in patients in whom the right ventricular pressure returned nearly to normal, the heart returned to within normal size within the first postoperative year and, thereafter, the heart grew normally with the growth of the chest.

It was of great interest that, in all patients in whom the right ventricular pressure was reduced below 100 mm. Hg, even though the pressure remained above 60 mm. Hg, the heart showed a definite decrease in size and, thereafter, remained constant while the child grew. Therefore, over a period of years, the cardiothoracic ratio returned to normal.

In contrast to this finding, the 3 patients (nos. 4, 5, 13) in whom the postoperative pressure remained above 100 mm. Hg have been followed for more than 3 years and their hearts and chests have grown proportionately. Consequently, in these 3 patients, the cardiothoracic ratio has remained constant. None have shown evidence of progressive enlargement but, nevertheless, enlargement persists.

These observations indicate that a pressure of approximately 100 mm. Hg seems to be the critical level as far as the size of the heart is concerned. If the right ventricular pressure is reduced to less than 100 mm. Hg, the heart decreased in size or remained stationary while the chest grew.

Summary

Transventricular pulmonary valvulotomy was performed at the Johns Hopkins Hospital on 86 patients with pulmonary valvular stenosis and an intact ventricular septum. There were 7 deaths, a mortality rate of 8.1 per cent, which includes 1 patient who died of a brain abscess and 2 patients who had previously had anastomotic procedures for an erroneous diagnosis of a tetralogy of Fallot. Of the 79 surviving patients, 8 have not had adequate follow up study. Among the remaining 71 patients, there are 2 patients who had previously been operated upon for a tetralogy of Fallot. The analysis, therefore, deals primarily with 69 patients who have been followed from 3 months to 4 years postoperatively, all of whom had been operated upon prior to November 1953.

Subjective improvement was noted in all but 2 patients. The comparison of the hemograms and arterial oxygen saturations shows improvement in all patients except 1, in whom an associated anomaly of the pulmonary venous return is suspected.

The analysis of the postoperative physical findings showed the murmur to be less intense in 24 patients and the disappearance of a systolic thrill in 14 of these patients. In 15 patients, a diastolic murmur was heard in the pulmonic area. Engorgement of the liver was not noted in any patient after valvulotomy and, in every instance in which pulsations at the liver edge were present preoperatively, the pulsations ceased almost immediately following operation.

Changes in the size of the heart, both in the immediate and late postoperative periods, were studied. The results showed that if the heart was not enlarged preoperatively, there was no change in the size of the heart, whereas, when the heart was enlarged, several distinct types of change were noted. In patients under 2 years of age, there was an actual increase in the size of the heart in the immediate postoperative period. Later examinations, however, showed the heart to have remained stationary while the chest grew; thus, ultimately, there was decrease in the cardiothoracic ratio. In patients over 18 years of age, the heart decreased steadily in size during the first few postoperative months. In some of the younger patients, the size of the heart decreased to within normal limits and then grew normally with the growth of the chest; in others, the heart remained the same size while the chest grew, so that the cardiothoracic ratio decreased until the heart returned to normal size; in still others, only progressive enlargement ceased; the heart and chest grew together and the cardiothoracic ratio remained unchanged.

Analysis of the cardiac catheterization showed a correlation between the postoperative pressure and the change in the size of the heart. Those patients in whom the pressure was reduced to below 100 mm. Hg, the size of the heart returned to normal. These patients were considered to have obtained an excellent result from surgery.

SUMMARIO IN INTERLINGUA

In le curso de quatro annos, valvulotomia pulmonar transventricular esseva executate al hospital Johns Hopkins in 86 patientes con stenosis pulmono-valvular e intacte septo ventricular. Occurreva 7 mortes. Isto esseva un mortalitate de 8,1 pro cento, includente un patiente qui moriva ab un abscesso cerebral e 2 patientes previemente subjicite a interventiones anastomotic post erronee diagnoses de tetralogia de Fallot. Le gruppo de 79 superviventes include 8 con inadequate observationes postoperatori. Duo del remanente 71 patientes habeva previemente essite subjicite a operationes pro tetralogia de Fallot. Per consequente le analyse se concerne primarimente con un gruppo de 69 patientes. In lor casos le observationes post-operatori occupava periodos de inter 3 menses e 4 annos.

Melioration subjective esseva reportate in omne casos con 2 exceptiones. Le comparation del hemogrammas e del saturationes oxygenic revela melioration in omne patientes con un exception. Isto concerne un patiente in qui il ha un suspicite anomalia del retorno pulmonovenose.

Le analyse del postoperatori observationes physic monstrava murmures de intensitate reducite in 24 patientes. In 14 de iste casos, etiam le disparition de un fremito systolic esseva constatate. In 15 patientes un murmure diastolic esseva audibile in le area pulmonic. Turgescentia del hepate non esseva notate in ulle patiente post le execution de valvulotomia, e in omne casos in que pulsationes del margine hepatic esseva presente ante le operation, iste pulsationes cessava quasi immediatemente post le operation.

Alterationes in le dimensiones cardiac esseva studiate tanto immediatemente como etiam plus longemente post le operation. Le resultatos monstrava que si le corde non esseva allargate ante le operation, il habeva nulle alterationes del dimensiones cardiac. In le casos in que le corde habeva essite allargate ante le operation plure typos de alteration esseva distinguibile. In patientes de etates de minus que 2 annos, il habeva de factor un augmento del dimensiones del corde in le periodo immediatemente post le operation. Examines executate plus tarde monstrava, nonobstante, que le dimensiones del corde habeva remanite constante durante que le thorace se expandeva. Ultimemente il habeva consequentemente un reduction del proportion cardio-thoracic. In patientes de plus que 18 annos, le dimensiones del corde decresceva uniformemente durante le prime menses post le operation. In certes inter le plus juvene patientes, le dimensiones del corde decresceva usque a valores intra le limites normal, e postea illos cresceva normalmente con le crescentia del thorace. In altere casos le corde non alterava su dimensiones durante le crescentia del thorace, de maniera que le proportion cardio-thoracic decresceva usque le dimensiones del corde esseva normal. In ancora altere casos, solmente le allargamento progressive se arrestava. Le corde e le thorace cresceva parallelmente e le proportion cardio-thoracic remaneva stabile.

Le analyse de catheterisation cardiac revelava un correlation inter le pression postoperatori e le alterationes del dimensiones cardiac. In le patientes in qui le pression se reduceva usque a infra 100 mm Hg, le dimensiones del corde retornava a valores normal. Iste patientes, in nostre opinion, habeva derivate excellente beneficios ab le intervention chirurgic.

REFERENCES

[1] BROCK, R. C.: Pulmonary valvulotomy for relief of congenital pulmonary stenosis. Brit. M. J. **1:** 1121, 1948.

[2] SELLORS, T. H.: Surgery of pulmonary stenosis; a case in which the pulmonary valve was successfully divided. Lancet, **1:** 988, 1948.

[3] BLOUNT, S. G., JR., MCCORD, M. C., MUELLER, H., AND SWAN, H.: Isolated valvular pulmonic stenosis. Clinical and physiological response to open valvuloplasty. Circulation **10:** 161, 1954.

[4] LANDTMAN, B.: Postoperative changes in the electrocardiogram in congenital heart disease. I. Pure pulmonary stenosis. Circulation **10:** 859, 1954.

[5] TAUSSIG, H. B., AND GOLDENBERG, M.: Roentgenologic studies in the size of the heart in childhood; 3 different types of teleorentgenographic changes which occur in acute rheumatic fever. Am. Heart J. **21:** 440, 1941.

[6] SOULIE, P., JOLY, F., CARLOTTI, J., SICOT, J. R., AND VOCI, G.: Étude physiopathologique postoperatoire de la trilogie de Fallot: Étude neuf cas apres valvulotomie pulmonaire. Arch. mal. coeur. **45:** 385, 1952.

Blood Pressure Studies Among American and Foreign-Born Students

By NÁNDOR SZENT-GYÖRGYI, M.D.

The relation of hypertension to race, sex, environment, and geographic origin in a young adult population is analyzed. Of the 3508 university students, 6.7 per cent were hypertensive. Among American men and women the incidence was 8.1 per cent and 3.1 per cent, respectively. The incidence of hypertension in all racial groups is significantly higher among American-born than among foreign-born males. After 10 years of residence in the United States, foreign-born students have the same high incidence of hypertension as those born in the United States and Canada. Detailed study is presented regarding the incidence of hypertension in different age groups among American and foreign-born white, Negro and Asian students.

TO CONTRIBUTE to the knowledge of the relationship between essential hypertension and climate, race, nutrition, occupation, and way of life, a selected group of people were investigated. One part of this investigation is presented in this paper. The group examined represents a little condensed world of men and women of various races (white, Negro, Asian, etc.), who are natives of five continents. It is a selected group in so far as they are college and graduate students with an above-average educational level, conducting sedentary lives, practically without any regular physical work. This is a group of the intellectual elite, the future leaders of America and of the other countries all over the world. Therefore, it would seem of importance to evaluate the physical condition and fitness of this group of people. A detailed study dealing with the connection and relationship of essential hypertension to sex, origin, race, climate, and residence is presented.

SCOPE AND MATERIALS

The blood pressure records of 3508 students of the University of Chicago were studied. These students were enrolled in the Summer quarter of 1954. Nobody was included in the study with any evidence of heart disease, diabetes, hyperthyroidism, or hormonal dysfunction. All patients with hypertension who also had albuminuria were excluded from the study, even those with supposed orthostatic albuminuria. All otherwise healthy students who did not have any clinical symptoms and had a grade A health rating were included in the study. In this way the number of investigated cases undoubtedly was reduced a great deal, but one could be sure that all organic diseases with a possible elevated blood pressure were excluded.

The blood pressure was determined at the entrance examination, and when it was found to be elevated, the student was usually recalled for one or more subsequent blood pressure determinations. Diehl and Hessdorfer[1] are of the opinion that young men who have an elevated blood pressure, even though it be transient, are more likely to have high blood pressure after 5 to 10 years than men whose blood pressure at the earlier ages was consistently within the so-called normal limits. Furthermore, Schroeder[2] states that hypertension is not uncommon in young adults in the United States and, according to Page and Corcoran,[3] many of the young people with transitory elevation of arterial tension will sooner or later develop essential hypertension.

The geographic location of the birthplace, the duration of residence in America, and the race were determined from the data furnished by the students themselves. Everybody who was born in the continental United States or in Canada was considered as American born. American citizens born outside the continental United States (e.g., in Hawaii or Puerto Rico) were listed among the foreign born, which is

From the Department of Medicine and Student Health Service, University of Chicago Medical School, Chicago, Ill.

quite proper in a paper dealing with influences of climate, origin, and environment upon a disease.

The importance of hypertension in young adult life is emphasized by the fact that the disease is generally more severe in younger patients; they die sooner.[4] According to Palmer and Muench[5] the unfavorable effect of hypertension on mortality is highest in persons in the younger age group and decreases rapidly with advancing age. Palmer's[6] studies at Harvard University revealed that slightly more than 10 per cent of the young male adults had systolic pressures above 140 mm. Hg. Alvarez, Wulzan, and Mahoney,[7] found that "hypertension is very common among young men, 22 per cent having systolic pressures exceeding 140 mm."

Others, however, like Robinson and Brucer[8] set the limits of the normal blood pressure as low as 120/80 mm. Hg, stating, "blood pressure over 120/80 is abnormal at any age and bespeaks incipient hypertension." On the other hand, Master, Garfield, and Walters[9] found the upper limits of the normal blood pressure definitely higher than the commonly accepted ones, these limits varying with sex and age. According to Master, in males the normal range of systolic pressure at 16 years of age is 105 to 135 mm. Hg. At 19 years of age the range increases to 110 to 140; at 40 years, to 110 to 150, and at 60 years of age, to 115 to 170 mm. Hg. Fishberg[10] has recently expressed the opinion that the upper limit of the normal blood pressure is 140/90 or less. Schroeder[2] also has used the 140/90 limit in his studies.

We have chosen the generally accepted limit of 140/90 mm. Hg in this study, thus avoiding the extremes and recognizing that it may be too high for young women.

In our material most of the elevated blood pressure readings fell in the 140 to 160 mm. range, and out of the 236 hypertensive cases only 7, or 2.9 per cent, had systolic pressures higher than 160 mm.

In the following pages, the role of sex, race, and geographic origin are discussed in detail.

Results and Discussion

Table 1 shows that 3508 students were examined for hypertension (2715, or 77.4 per cent men, and 793, or 22.6 per cent women). Among the students 3056, or 87.1 per cent, were American born and 452, or 12.9 per cent, foreign born. Among the Americans, 96.4 per cent were white, of whom 77.8 per cent were males and 22.2 per cent were females. American born nonwhite subjects were represented by 3.5 per cent only. In the foreign-born group the ratio was quite different; 71.9 per cent white subjects of whom 76.3 per cent were males and 23.7 per cent were females, and 28.1 per cent nonwhite subjects of whom 79.5 per cent were males and 21.5 per cent were females. The Asian-born population represented 25.4 per cent of the total foreign-born students. The ratio of male to female population was in all 3 groups about the same, in spite of the big differences in absolute numbers.

Table 2 shows that 6.7 per cent of all students were hypertensive; 7.7 per cent were male and 3.2 per cent were female. Boynton and Todd[11] found 7.31 per cent hypertensive men and 1.41 per cent hypertensive women among university students.

Seven per cent of the American students and 4.6 per cent of the foreign-born students were hypertensive. There was no significant difference among the American and the foreign-born female students (3.1 and 3.8 per cent, respectively), but there were far more hypertensives (8.1 per cent) among the American men than among foreigners (4.9 per cent). Expressed in percentages: the incidence of hypertension was about 60 per cent higher among young American men than among foreign born men. If the incidence would be the same (4.9 per cent) as among the foreigners, there would be 116 hypertensive American men instead of the 193, as found. This lower incidence of hypertension among foreign born men is the more striking, since the foreign students were under more stress and tension than the Americans at the beginning of their studies.

The breakdown of the figures according to the race and geographic origin (which includes such factors as climate and nutrition besides race) is given in table 3.

In table 3 there was no difference between American and European whites, both groups having 6.9 per cent hypertensives. The addition of the white Europeans and the white non-Euro-

TABLE 1.—*Analysis of Material According to Origin, Race, and Sex*

American born			Foreign born		
Subject	No. of Cases	Percentage	Subject	No. of Cases	Percentage
White			White		
Men	2297	97*	European men	186	53.2†
Women	652	94.4	European women	60	58.2
Total	2949	96.5	Non-European men	62	17.7
			Non-European women	17	16.5
			Total	325	71.9
Negro			Asiatic		
Men	51	2.1	Men	92	26.3
Women	31	4.5	Women	23	22.3
Total	82	2.6	Total	115	25.4
Asian			African		
Men	16	0.7	Men	7	2.0
Women	6	0.9	Women	1	0.9
Total	22	0.7	Total	8	1.7
American Indian			South American Negro		
Men	2	0.09	Men	2	0.6
Women	1	0.1	Women	2	1.9
Total	3	0.09	Total	4	0.9
Total men	2366	67.4	Total men	349	9.9
Total women	690	19.6	Total women	103	3.0
Total men and women	3056	87.1	Total men and women	452	12.9

Total subjects: 3508; total men: 2715 or 77.4 per cent; total women: 793 or 22.6 per cent

* In terms of the inclusive numbers of the corresponding American-born groups (2366, 690, 3056, respectively).
† In terms of the inclusive numbers of the corresponding foreign-born groups (349, 103, 452, respectively).

peans gave 5.8 per cent, which still was not a significant difference. However, the incidence of hypertension among the non-European white men was only 3.2 per cent, which was less than half that of the white Europeans. The percentage of American white hypertensive men exceeded that of the non-European white men by a factor of 2.5. The latter group included—in regard to geographic location and background of civilization—very wide variations (from Israel to Australia, from South Africa to South America). There seems to be a common causative factor responsible for the higher incidence of hypertension in North America and in Europe, which was not observed on other continents.

American Negro men were represented by 15.6 per cent hypertensive students and African born non-whites (Negro) by 14.2 per cent. According to the American Heart Association,[12] between 1915 and 1950 the death rates from cardiovascular disease for the nonwhite population were invariably higher than for the white. It was stated recently in a panel discussion[4] that hypertension is more common in

TABLE 2.—*Hypertension According to Sex and Origin*

	No. of Cases	Percentage
Hypertensive	236	6.7 of 3508
Men	210	7.7 of 2715
Women	26	3.2 of 793
Birthplace		
American born	215	7.0*
Men	193	8.1*
Women	22	3.1
Foreign born	21	4.6*
Men	17	4.9*
Women	4	3.8

* These differences, 7.0% *versus* 4.6% and 8.1% *versus* 4.9%, are statistically significant ($\chi^2 = 8.19$ and 4.64, respectively; $p = <0.01$ and <0.05, respectively).

TABLE 3.—*Hypertension According to Race and Geographic Origin*

	No. of Cases	Percentage		No.	Percentage
American born			Foreign born		
White men*	184	8.0	European white men	13	6.9
White women	21	3.2	European white women	4	6.6
White total	205	6.9	European white total	17	6.9
			non-European white men	2	3.2
			non-European white women	0	0
			All whites	19	5.8
Negro men*	8	15.6	African men	1	14.2
Negro women	1	3.2	African women	0	0
Asian men	1	6.2	Asian men	1	1.0
Asian women	0	0	Asian women	0	0
Indian men and women	0	0	South American Negro men and women	0	0

* American white men have an incidence of hypertension of 8.0 per cent and American Negro men of 15.6 per cent. The difference is statistically significant, because the difference is twice the standard error. (Standard error of the difference between the two proportions in this case = 3.8.)

Negroes than in Caucasians. Ornstein[13] found the incidence of hypertension in young Negroes higher than in white persons of similar age groups. The ratio of rejection from the Armed Services due solely to hypertension was 3.47 per cent in Negroes as compared to 1.01 per cent in white men. According to Schroeder,[2] hypertension is more common in American Negroes than in white Americans. While the number of Negroes included in this study was too small for any definite conclusions, it was in perfect agreement with the findings of other authors on the higher incidence of hypertension in American Negroes. In our analysis, the same was true for the African-born nonwhite men, and although statistically insignificant, it compared with the findings in American-born Negroes. Donnison[14] reported that over a period of two years at a native hospital in Kenya approximately 1800 patients were admitted, and no case of elevated blood pressure was encountered. Certainly our students from Africa were not primitive but highly civilized individuals, which fact may be important in respect to blood pressure. In this connection reference should be made to Hartnett and Ratcliffe,[15] who quoted from Dubois an incidence of 35.5 per cent for hypertension among 200 Congo natives.

Low blood pressure values have been reported from the Orient, particularly from China. Foster[16] found that the blood pressure of Occidentals living in China, in the majority of the persons studied, was lower in China than it used to be while in America. Blood pressure of Chinese has been shown to be lower than the usual average, and hypertension is rare. This is proved in this study, too, since only 1 per cent of Asian born men were found to be hypertensive as compared with an incidence of 6.9 per cent in European men and 8 per cent in American white men. In this connection, in our material, 6.2 per cent of the American born Asian men have hypertension. This is a striking difference. It seems to indicate that climate and environment have a strong influence on blood pressure. Krakower[17] found the same effect of climate on long-time Chinese residents in Canada; he stated that among these Chinese hypertension is not uncommon.

In table 4, are listed hypertensive cases according to age groups.

It is not surprising that the absolute number of hypertensive cases is higher in the younger age group than in the older one, since the majority of the subjects studied obviously fell in the younger age group. However, the extraordinary difference is surprising, if one compares the incidence among men and women, since the general distribution of men and women according to age groups was about the same. In spite of the fact that the largest part

TABLE 4.—*Hypertension According to Age Groups*

Age Group	<20		21–30		31–40		>41 Years	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
American born								
White men	72	39.1	93	50.5	17	9.2	2	1
White women	2	9.5	5	23.8	4	19	10	47.6
Negro men	1	12.5	4	50.0	3	37.5	—	—
Negro women	—	—	—	—	—	—	1	100
Asian men	—	—	1	100	—	—	—	—
American total men	73	37.8	98	50.7	20	10.3	2	1
American total women	2	9	5	22.7	4	18.1	11	50
Foreign born								
European men	2	15.3	8	61.5	2	15.3	1	7.7
European women	—	—	1	25	2	50	1	25
White non-European men	—	—	2	100	—	—	—	—
Asian men	—	—	—	—	1	100	—	—
African men	—	—	1	100	—	—	—	—
Foreign born total men	2	11.7	11	64.7	3	17.6	1	5.8
Foreign born total women	—	—	1	25	2	50	1	25
Total men	75	35.7	109	51.9	23	10.9	3	1.5
Total women	2	7.6	6	23	6	23	12	46.1

	<30 years	>31 years
American men	88.7%	11.3%
American women	31.5%	68.2%
Foreign-born men	76.5%	23.5%
Foreign-born women	25.0%	75.0%
Total men	87.6%	12.4%
Total women	30.7%	69.3%

TABLE 5.—*Foreign Born According to the Years Spent in America*

	I 0–1	II 1–10	III 10 or more yrs.	IV 10 yrs. or less	V 1 yr. or more
Total	208 or 46%	150 or 33.2%	94 or 20.7%	358 or 79.3%	244 or 54%
Hypertensive from total	8 or 3.8%	5 or 3.3%	8 or 8.5%*	13 or 3.6%*	13 or 5.3%

* The difference between 3.6% and 8.5% is statistically significant[18]. ($\chi^2 = 4.03$; p = 0.02 to 0.05).

of the student population was below 30 years of age, the overwhelming percentage of the female hypertensive students fell in the older (above 30 years) age group. This was true whether one analyzed separately the American and foreign-born students, or the total. Of the hypertensive men, 87.6 per cent were below 30 in age and 12.4 per cent were older. The reverse was true for women, with 30.7 per cent of the hypertensive women under 30 years of age, and 69.3 per cent above 30. There was no significant change in the picture if one analyzed the findings for the various racial groups.

Tables 5 and 6 consist of a breakdown of the foreign-born students according to the years spent in America prior to the blood pressure readings.

Thirty eight per cent of the foreign-born *hypertensive* students spent one year or less in America (table 6) and 46 per cent of *all* foreign-born students lived in the United States less than 1 year (table 5). Thirty eight per cent of the foreign-born *hypertensive* students resided for 10 years or more in the United States, but only 20.7 per cent of *all* foreign-born students lived here longer than 10 years. These data

TABLE 6.—*Percentage Distribution of the Hypertensive Foreign Born Subjects According to the Length of Time Spent in America*

I 0–1 yr.	II 1–10 yr	III 10 or more yr.	IV 1 yr. or more
38%	24%	38%	62%

clearly indicate that the factors that raise the blood pressure in the foreign-born must be inherent in the American environment (climate, geographic location, nutrition, way of life, or combined). Furthermore, if we consider that the incidence of hypertension in foreigners with less than one year's residence was only 3.8 per cent and among those who lived in the United States for more than 10 years the rate was 8.5 per cent, i.e., over double the first group, little doubt remains regarding the importance of modifying factors in the development of hypertension, beyond the role of race.

In an analysis of the five columns of table 5 with regard to hypertension, there was no significant differences between groups I and II; however, the figure jumped to 8.5 per cent after 10 years of residence in America (group III), in spite of the fact that group I included 46 per cent, group II 33.2 per cent, and group III only 20.7 per cent of foreign-born students. The 358 students in group IV included 13 with hypertension (3.6 per cent), a rate which was less than half of the older residents in group III.

SUMMARY AND CONCLUSIONS

Of the 3508 students examined (2715, or 77.4 per cent men and 793, or 22.6 per cent women), 236, or 6.7 per cent, were hypertensive.

Among the students 3056, or 87.1 per cent, were American born and 452 or 12.9 per cent foreign born. Seven per cent of the American and 4.6 per cent of the foreign born were found to be hypertensive. The incidence of hypertension in American born students was significantly higher than among foreign born ones.

Hypertension was noted in 8.1 per cent of the American men and 3.1 per cent of the women; 4.9 per cent of the foreign born men and 3.8 per cent of the women had hypertension. Hypertension was more common in American-born men than women by a factor of 2.5.

The rate of hypertension was 6.9 per cent among the white Americans and Europeans. Eight per cent of the white American men and 3.2 per cent of the women were hypertensive. The rates were 6.9 per cent for the European men and 6.6 per cent for the European women, but only 3.2 per cent for the non-European white men and zero for the women. The incidence of hypertension among American men was significantly higher than among foreign-born men. There was no significant difference in the incidence of hypertension between American and foreign-born women.

There was no difference in the incidence of hypertension between American and European-born white students. However, the percentage among foreign-born non-European white men was less than half that of the American and European white men. American-born and African-born Negro men were represented with rates of 15.6 per cent and 14.2 per cent, respectively.

There was a higher incidence of hypertension in American Negro men than in any other group examined, topping the next highest group, the American white men by a factor of 2. Since the group of African-born Negro men was too small to be statistically significant, these data cannot contribute to the solution of the controversial findings and opinions regarding the incidence of hypertension among African Negroes.

The incidence of hypertension among American-born Oriental men was six times higher than among Asian-born Orientals, but still lower than among American or European-born white men.

Four-fifths of both the American and foreign-born hypertensive men were under 30 years of age. The reverse was true for the women; almost three-fourths of the hypertensive women were above the age of 30 years.

Of the foreign-born students, forty-six per cent had spent one year or less in this country, and the incidence of hypertension was 3.8 per cent among them; 33.2 per cent had spent 1 to 10 years in America and their incidence was 3.3 per cent. Only 20.7 per cent had spent more

than 10 years here prior to the examination, but they showed an incidence of 8.5 per cent, i.e., the same as among American-born white men.

Among foreign-born residents who had spent less than 10 years here, the incidence of hypertension was less than half of that of the residents who had spent over 10 years in the United States.

One gets the impression that if someone lives in the United States long enough—regardless of birthplace or race—he will stand the same chance of becoming hypertensive as if he had been born here.

American-born men in all racial groups have a higher incidence of hypertension than the corresponding groups of foreign-born men.

Summario in Interlingua

Esseva examinate 3508 studentes: 2715 masculos (77,4 pro cento) e 793 femininas (22,6 pro cento). Esseva trovate 236 hypertensivos (6,7 pro cento).

Le total consisteva de 3056 studentes nascite in America (87,1 pro cento) e 452 studentes nascite al estraniero (12,9 pro cento). Septe pro cento del studentes nascite in America e 4,6 pro cento del studentes nascite al estraniero esseva hypertensivos. Le frequentia de hypertension in studentes de nascentia american esseva significativemente plus alte que in studentes nascite al estraniero.

Hypertension esseva constatate in 8,1 pro cento del masculos american e in 3,1 pro cento del femininas american. Inter le studentes nascite al estraniero, 4,9 pro cento del masculos e 3,8 pro cento del femininas habeva hypertension. Inter le studentes de nascentia american, hypertension in masculos escedeva hypertension in femininas per un factor de 2,5.

Inter le americanos e europeos de racia blanc, hypertension habeva un frequentia de 6,9 pro cento. Octo pro cento del american masculos blanc e 3,2 pro cento del american femininas blanc esseva hypertensive. Le procentages correspondente pro masculos e femininas europee esseva 6,9 e 6,6 e pro masculos e femininas non-europee blanc solmente 3,2 e 0, respectivemente. Le frequentia de hypertension inter masculos american esseva significativement plus alte que inter masculos nascite al estraniero. Il non habeva un differentia significative in le frequentia de hypertension in femininas de nascentia american comparate con femininas nascite al estraniero.

Il habeva nulle differentia in le frequentia de hypertension in studentes blanc nascite in America in comparation con le studentes blanc nascite in Europa. Sed inter le studentes non-europee blanc, le procentage pro masculos esseva minus que un medietate del procentage inter le masculos blanc de nascentia europee e american.

Masculos negre nascite in America e masculos negre nascite in Africa monstrava procentages de 15,6 e 14,2, respectivemente.

Le frequentia de hypertension in masculos negre nascite in America esseva plus alte que le frequentia de hypertension in ulle altere gruppo examinate. A parte le gruppo de negros nascite in Africa, le negros nascite in America habeva un frequentia de hypertension excedente per un factor de 2 le frequentia de hypertension inter american masculos blanc (qui constitueva le secunde gruppo in le ordine del frequentias). Proque le masculos negre de nascentia african non esseva satis numerose pro esser statisticamente significative, nostre datos non pote contribuer a un resolution del controversia (de observationes e opiniones) relative al frequentia de hypertension inter negros african.

Le frequentia de hypertension inter masculos oriental de nascentia american esseva sex vices plus grande que inter masculos oriental nascite in Asia sed nonobstante plus basse que inter masculos blanc de nascentia american o europee.

Quatro quintos del masculos hypertensive, tanto american como etiam de nascentia estranier, habeva minus que 30 annos de etate. Inter le femininas le tendentia esseva le contrario: quasi tres quartos del femininas hypertensive habeva plus que 30 annos de etate.

Le studentes nascite al extero de America includeva 46 pro cento qui habeva passate un anno o minus in iste pais. Pro illes le frequentia de hypertension esseva 3,8 pro cento. Pro le gruppo qui habeva passate inter 1 e 10 annos in America, le correspondente procentages

esseva 33,2 e 3,3. Solmente 20,7 pro cento habeva habitate America durante plus que 10 annos ante le tempore del examine de lor pression sanguinee, sed illes monstrava un frequentia de hypertension de 8,5 pro cento, i.e. le mesme frequentia etiam constatate inter masculos blanc de nascentia american.

Inter individuos de nascentia estranier qui habeva passate minus que 10 annos in iste pais, le frequentia de hypertension esseva minus que un medietate del frequentia de hypertension inter illes qui habeva passate plus que 10 annos in America.

On ha le impression que si un subjecto vive satis longe in le Statos Unite, ille ha—sin reguardo a loco de nascentia o a racia—le mesme prospectos de disveloppar hypertension como si ille habeva nascite in le Statos Unite.

Masculos nascite in America, de non importa qual aggruppamento racial, ha un plus alte frequentia de hypertension que masculos del mesme racia nascite al estraniero.

REFERENCES

[1] Diehl, H. S., and Hessdorfer, M. B.: Blood pressure in young men over a 7-year period. Arch. Int. Med. **52:** 948, 1933.

[2] Schroeder, H. A.: Hypertensive Diseases. Philadelphia, Lea and Febiger, 1953, p. 52.

[3] Page, I. H., and Corcoran, A. C.: Hypertensive Vascular Disease. *In*, Therapeutics in Internal Medicine, Kyser, F. A., Ed. New York, Harper and Brothers, 1953, p. 493.

[4] Panel Discussion: Treatment of Hypertension. Moderator: Wilkins, R. W., American College of Physicians, 39th Annual Session, Chicago, 1954.

[5] Palmer, R. S., and Muench, H.: Course and prognosis of essential hypertension. J. A. M. A. **153:** 1, 1953.

[6] —: Significance of essential hypertension in young male adults. J. A. M. A. **94:** 694, 1930.

[7] Alvarez, W. C., Wulzan, R., and Mahoney, L. J.: Blood pressures in 15,000 university freshmen. Arch. Int. Med. **32:** 17, 1923.

[8] Robinson, S. C., and Brucer, M.: Range of normal blood pressure; statistical and clinical study of 11,383 persons. Arch. Int. Med. **64:** 409, 1939.

[9] Master, A. M., Garfield, C. I., and Walters, M. B.: Normal Blood Pressure and Hypertension, New Definitions. Philadelphia, Lea and Febiger, 1952.

[10] Fishberg, A. M.: Differential diagnosis of high blood pressure. M. Clin. North America. **38:** 753, 1954.

[11] Boynton, R. E., and Todd, R. L.: Blood pressure readings of 75,258 university students. Arch. Int. Med. **80:** 454, 1947.

[12] American Heart Association Statistical Handbook: Diseases of the Heart and Blood Vessels —Facts and Figures. 1954. Revised edition.

[13] Ornstein, L. L.: Hypertension in young Negroes. War Med. **4:** 422, 1943.

[14] Donnison, C. P.: Blood pressure in the African native. Lancet **1:** 6, 1929.

[15] Hartnett, W. G., and Ratcliffe, H. E.: Study in hypertension on Southern Negroes. South. M. J. **41:** 847, 1948.

[16] Foster, J. H.: Blood pressure of foreigners in China. Arch. Int. Med. **40:** 38, 1927.

[17] Krakower, A.: Blood pressure in Chinese living in Eastern Canada. Am. Heart J. **9:** 396, 1934.

[18] Hill, A. B.: Principles of Medical Statistics. New York, Oxford University Press 1950, p. 127.

To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.—William Osler. *Aequanimitas and Other Addresses*. Philadelphia, Blakiston & Co., and London, T. K. Lewis, 1904.

The Angiocardiographic Diagnosis of Left Atrial Thrombosis

By Louis A. Soloff, M.D., and Jacob Zatuchni, M.D.

With the advent of modern cardiac surgery the clinical diagnosis of intramural thrombi, ball valve thrombi and myxomatous and other tumors in the left atrium has assumed great importance. It is shown here that a diagnosis of thrombosis within the left atrium is possible by angiocardiography. The angiocardiographic features of mural and ball valve thrombi of the left atrium and of left auricular thrombosis are described.

THROMBI in the left atrium have been definitively diagnosed during life, in the absence of cardiac surgery, only in those very rare instances when they were sufficiently calcified to be visible on conventional roentgenograms.[1, 2] We report herein for the first time, so far as we are aware, their visualization by angiocardiography. We found five instances in our first 57 studies, an incidence of 8.8 per cent. This incidence may be compared to that found at autopsy in patients with mitral stenosis, which is variously reported to be between 8 and 15 per cent[3-6] (excluding those thrombi localized to the left auricle). Considering that our patients are obviously in an earlier stage of the rheumatic disease than those that come to autopsy and the occasional confusion of agonal or postmortem clots with antemortem thrombi, we believe that our angiocardiographic incidence of intra-atrial thrombi is close to the actual incidence of such thrombi in our series of patients.

Of the 5, 2 were verified at operation and one at autopsy. Surgery was not performed in one patient, primarily because of our angiocardiographic findings. The last had no preoperative angiocardiogram. A thrombus, which was found but not removed at surgery, was demonstrated later by angiocardiography.

Case Reports

Case 1. E. W., a 49 year old woman, entered the Episcopal Hospital on March 4, 1955, because of dyspnea. She had chorea at 9 and a right hemiparesis since the age of 15, when a cerebral embolus occurred 12 days after delivery of her first pregnancy. Since her tenth and last pregnancy at 36, she has had intermittent dyspnea and weakness.

Examination revealed slight enlargement of the heart, atrial fibrillation, accentuated pulmonic second sound and a faint apical diastolic rumble. The jugular veins were slightly distended. The liver was slightly enlarged.

Roentgenographic study showed a slightly enlarged cardiac silhouette. The pulmonary segment was convex. The right ventricle and left atrium were enlarged. The pulmonary vascular markings were increased. An electrocardiogram showed atrial fibrillation, rightward deviation of QRS, and nonspecific ST-T changes.

An angiocardiogram was done on March 14, 1955. The superior vena cava time was 2.8 seconds, the right heart time 20.3, the pulmonary artery time 18.9, the left atrial time 13.3 and the intracardiac circulation time 9.8. The right atrium, right ventricle and pulmonary artery were enlarged. The left atrial volume was 303 ml. The left auricle was not opacified and was irregularly marginated from the opacified left atrium. Large filling defects were observed in the opacified left atrium, on the right, superiorly and inferiorly, and also posteriorly (fig. 1). The left ventricle was opacified to a lesser degree than the left atrium.

Mitral valvotomy was done on March 28, 1955, by Dr. Thomas J. E. O'Neill. The left auricle was enlarged and obliterated by organized thrombi. A large mural thrombus was felt along the posterior wall of the left atrium and could not be removed.

The angiocardiographic study was repeated 2 weeks after surgery and the filling defects in the left atrium were again observed.

Case 2. M. G., a 40 year old woman, entered Temple University Hospital on Sept. 12, 1955, because of progressive dyspnea and weakness.

Examination revealed moderate cardiomegaly, atrial fibrillation, accentuated pulmonic second sound and grade 2 systolic and moderate rumbling diastolic apical murmurs. Other than slight distention of the jugular veins, there were no signs of heart failure.

Roentgenographic study disclosed a moderate in-

Supported in part by a grant from the Southeastern Branch of the Heart Association of Pennsylvania.

crease in size of the cardiac silhouette. The pulmonary segment was convex. The left atrium and right ventricle were enlarged. The pulmonary vascular markings were increased. An electrocardiogram showed atrial fibrillation, rightward deviation of QRS and nonspecific ST-T changes.

Cardiac catheterization on Sept. 19, 1955, (done by Dr. George E. Mark, Jr.), revealed a pressure in the pulmonary artery of 60/26 mm. Hg and, in the right ventricle, 64/5 mm. Hg. The cardiac output was 3.5 L./min.

Angiocardiography immediately afterward showed a prolongation of all circulation times. The superior vena cava time was 7.0 seconds, the

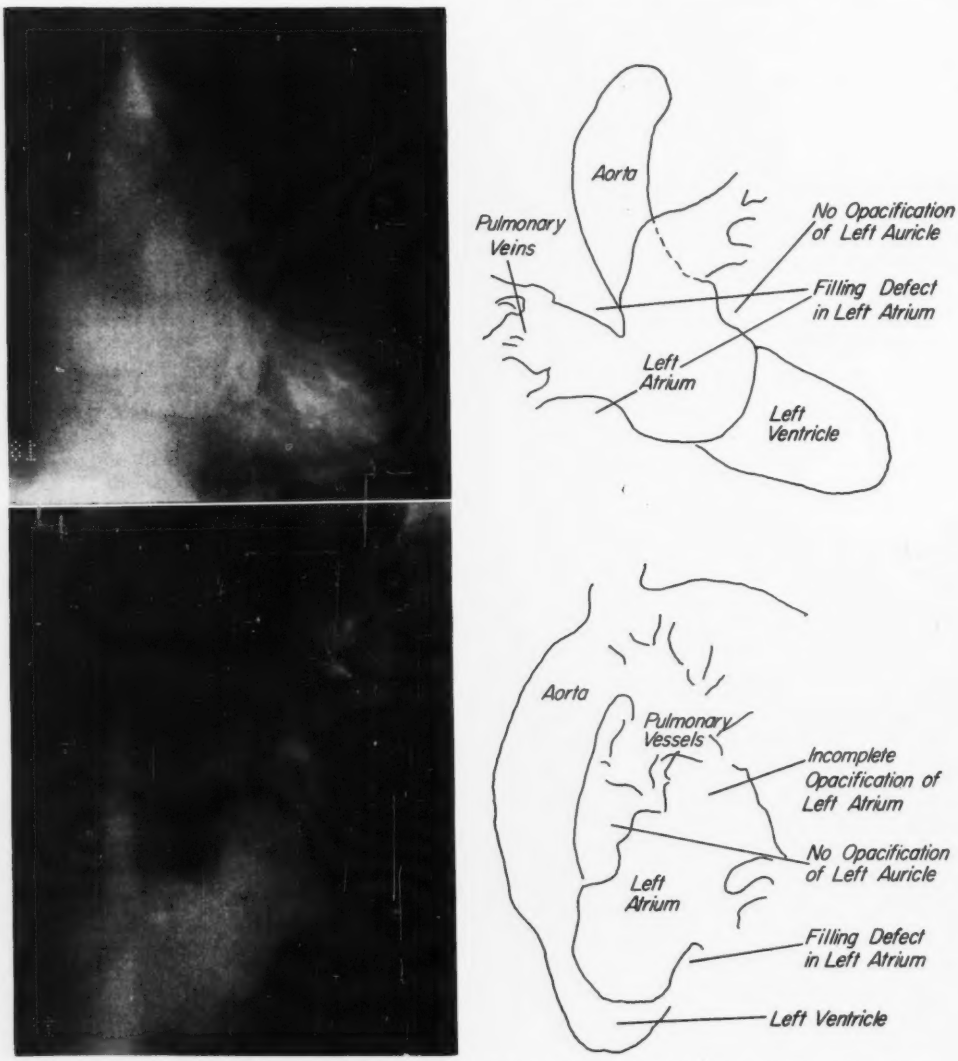


FIG. 1. Case 1. Simultaneous angiocardiograms in the anterior and left lateral projections, 11.2 seconds from initial opacification of the right atrium. The region of the left auricle is not opacified. There is irregular margination of the opacified left atrium at its auricular junction. In the anterior projection, note the filling defects in the opacified left atrium on the right, superiorly and inferiorly. In the lateral projection, there is sparse opacification of the left atrium superiorly and a filling defect along the posterior wall immediately above the region of the mitral valve.

right heart time 19.6, the pulmonary artery time 16.8, the left atrial time 17.7 and the intracardiac circulation time 18.2. The right atrium and ventricle, pulmonary artery and its branches were enlarged. The left atrial volume was 621 ml. Neither the left auricle nor the left ventricle was visualized. The border between the left auricle and atrium was irregularly marginated. There were large irregular filling defects protruding from the posterior wall of the left atrium in the lateral projection only (fig. 2).

Mitral valvotomy was done on Sept. 27, 1955, by Dr. George Rosemond. The left auricle was obliterated by organized thrombi. A clot was encountered by the finger entering the left atrium. Some of the clot spurted out and the remainder was flushed out. Following mitral valvotomy, it was thought that the left atrium was free of thrombus. Immediately after surgery, a saddle embolus was recognized and removed.

Two weeks later, angiocardiography again showed filling defects in the left atrium.

Case 3. A. F., a 28 year old woman with rheumatic heart disease and multivalvular involvement, entered Temple University Hospital on June 18, 1955, because of fever and intractable heart failure precipitated by a septic pulmonary infarct with abscess formation. During hospitalization, she had transient atrial fibrillation and prolonged unconsciousness due to cerebral embolism.

Roentgenographic study revealed marked cardiomegaly and a very prominent pulmonary artery. The right ventricle and left atrium were enlarged. An electrocardiogram showed sinus rhythm, large broad P waves and right ventricular hypertrophy.

An angiocardiogram was done on Sept. 7, 1955, following subsidence of fever and restoration of consciousness. The superior vena cava time was 16.8 seconds, the right heart time 56.1, the pulmonary artery time 52.6, the left atrial time 42.1 and the intracardiac circulation time 26.8. There was marked enlargement of the superior vena cava, right atrium and ventricle and pulmonary artery. The left atrial volume was 420 ml. A round filling defect was seen in the anterior and superior portion of the left atrium in the lateral projection only (fig. 3).

Cardiac surgery was not done because of bacterial endocarditis. Two months later, she was readmitted to the hospital, dyspneic, cyanotic and pulseless. She died in eight hours.

At autopsy, an organized thrombus, the size of a golf ball, was found free in the left atrium (fig. 4). There was multivalvular involvement. Vegetations were present along the mitral valve.

Case 4. M. P., a 62 year old woman, was admitted to the Episcopal Hospital on Jan. 18, 1955, because of sudden left hemiplegia. She had rheumatic fever at 30, angina pectoris since the age of 55, and, at 60, a saddle embolus, confirmed by aortography.

The blood pressure was 180/100 mm. Hg. The heart was not enlarged. The pulmonic second sound was accentuated. Atrial fibrillation was present. There were no signs of failure.

The hemiplegia disappeared immediately following right stellate ganglion block.

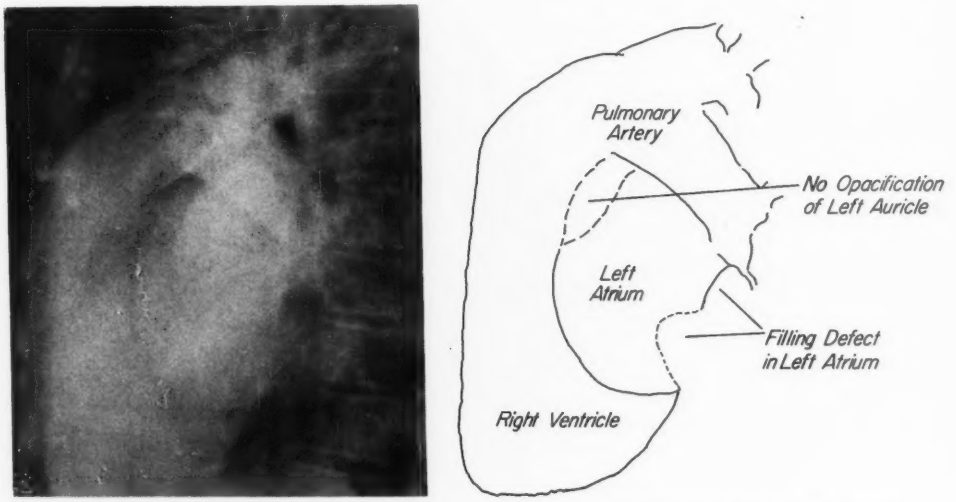


FIG. 2. Case 2. Angiocardiogram in the left lateral projection, 11.2 seconds from initial opacification of the right atrium. The left auricle is not opacified. There is irregular margination of the opacified left atrium at its auricular junction. There are filling defects along the posterior wall of the left atrium.

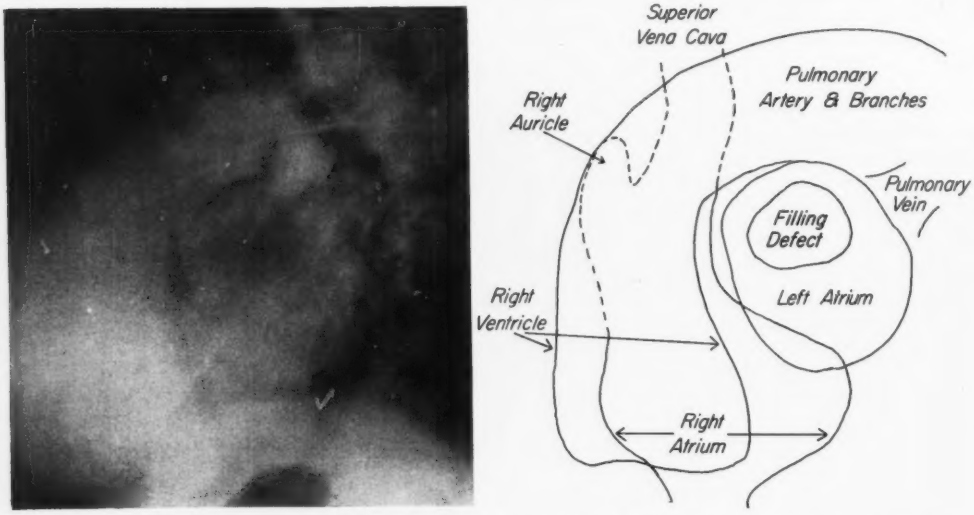


FIG. 3. Case 3. Angiocardiogram in the left lateral projection, 9.8 seconds from initial opacification of the right atrium. The left auricle is not seen and the auricular border of the opacified left atrium is smooth. Note the relatively round filling defect in the anterior, superior portion of the left atrium.

FIG. 4. The heart of case 3 at autopsy. Note the ball valve thrombus in the left atrium and the vegetations in the region of the mitral valve.

Roentgenographic study showed slight left atrial enlargement and prominence of the left second and third segments of the cardiac silhouette. An electrocardiogram showed atrial fibrillation and nonspecific ST-T changes.

An angiocardiogram was done on Feb. 1, 1955. The superior vena cava time was 5.6 seconds, the right heart time 20.3, the pulmonary artery time 18.9, the left atrial time 11.2 and the intracardiac circulation time 9.8. The left atrial volume was 303 ml. Filling defects were observed along the posterior wall of the left atrium, centrally and at the entrance of the right inferior pulmonary vein into the left atrium (fig. 5). The left auricle was not opacified and was irregularly marginated at its junction with the left atrium.

Cardiac surgery was considered unwise because of age, coronary artery disease and angiocardiographic findings.

Case 5. R. D., a 28 year old man, had polyarthritis and chorea at 11 and a cerebral embolus with right hemiparesis and transient atrial fibrillation at 25. Two years later, he entered the Episcopal Hospital for cardiac surgery.

Examination revealed right hemiparesis, slight cardiac enlargement, sinus rhythm, accentuated pulmonic second sound, pulmonary diastolic murmur and grade 2 systolic and moderate rumbling diastolic murmurs at the apex.

Roentgenographic study disclosed a slight increase in size of the cardiac silhouette with enlargement of the left atrium and right ventricle. The pulmonary artery segment was convex and the left third segment prominent. There was calcification of the mitral valve and of the posterior wall of the left atrium. An electrocardiogram showed findings consistent with left atrial disease and right ventricular hypertrophy.

Mitral valvotomy was done on Sept. 17, 1953, by Dr. Thomas J. E. O'Neill. The left auricle was thrombosed. Much of the superior portion of the left atrium was thrombosed and calcified. The thrombi could not be removed. There was calcification of the posterior wall of the left atrium and of the mitral valve.

Angiocardiography was done on Dec. 3, 1954, following recovery from a bout of heart failure. The superior vena cava time was 3.5 seconds, the right heart time 7.7, the pulmonary artery time 8.4, the left atrial time 12.6 and the intracardiac circulation time 8.4. The left atrial volume was 324 ml. The left auricle was not opacified. There was irregular margination of the left atrium superiorly. In the lateral projection, there were also large irregular filling defects in the left atrium posteriorly and superiorly (fig. 6).

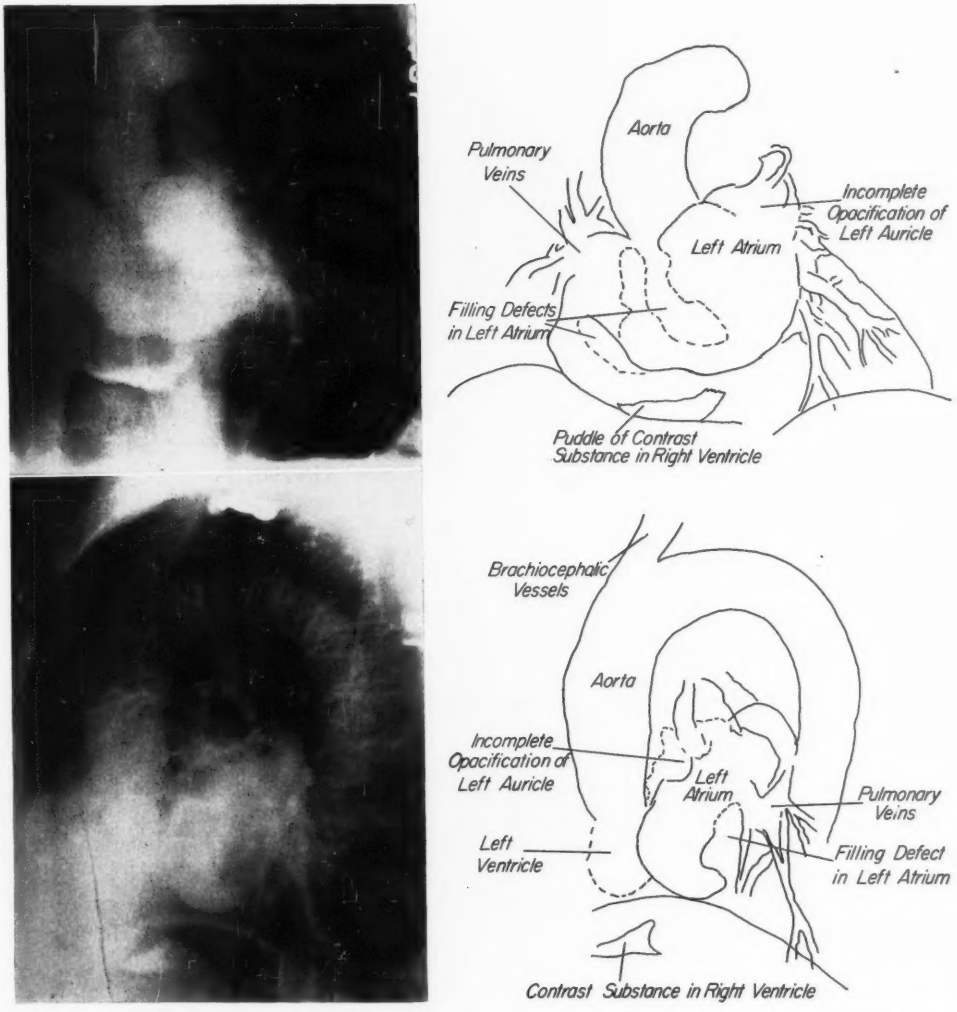


FIG. 5. Case 4. Simultaneous angiocardiograms in the anterior and left lateral projections, 14.0 seconds from initial opacification of the right atrium. The left auricle is sparsely opacified. The junction of the opacified left atrium and the auricle is irregular. Note the large filling defects in the left atrium in each projection.

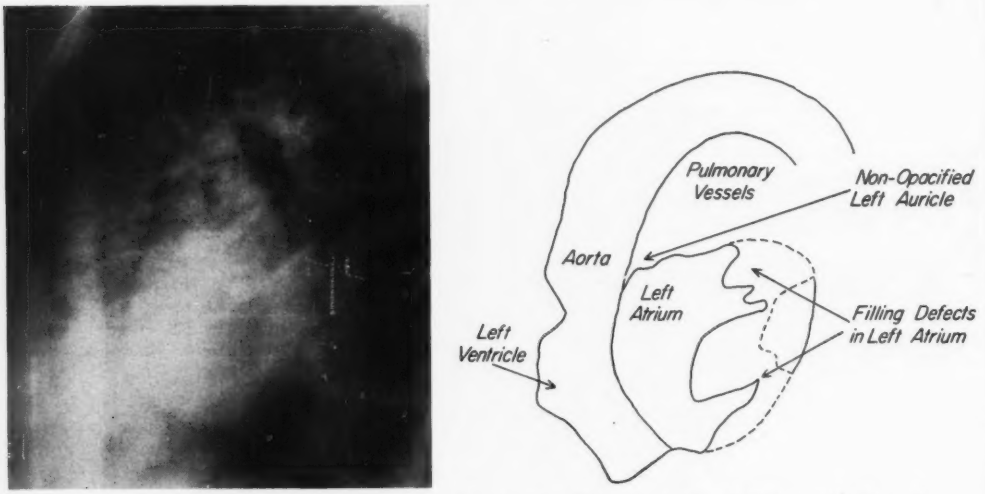


FIG. 6. Case 5. Angiocardiogram in the lateral projection, 16.1 seconds from initial opacification of the right atrium. The left auricle is not opacified. There is irregular margination of the opacified left atrium superiorly and also posteriorly. Note the large irregular filling defect within the left atrium and irregularity of the posterior wall of the left atrium immediately above the region of the mitral valve.

DISCUSSION

A retrospective diagnosis of thrombus within the left atrium is entertained when systemic embolization occurs in an individual with mitral stenosis. But one cannot be certain that the embolus actually arose from the left atrium or that a residual thrombus is present. Calcification of the posterior wall of the left atrium[7] is sometimes associated with an underlying thrombus, but thrombi are frequently present in the absence of such calcification. Prominence of the third left segment of the cardiac silhouette in the anterior projection[8] may also suggest a thrombus, but this finding is frequently present without a thrombus and, conversely, a thrombus is frequently present without this sign. Only calcification within the left atrium is diagnostic and this is very rare.

It has been stated that mural thrombi do not produce defects in the left atrium.[9] On the contrary, the left atrium is particularly suitable for angiocardiographic visualization of thrombi.

Opacification of the left atrium in mitral stenosis is intense, homogeneous and persists for longer than normal.[10] Any mass attached to the walls of the left atrium is easily visible, provided overlapping structures are eliminated and the projection is adequate. We have found the posterior-anterior and left lateral projections best for avoiding overlapping of opacified structures. The simultaneous biplane angiocardiographic apparatus of Chamberlain, which we use, permits not only two projections at right angles but also stereoscopic pairs that aid in the differentiation of extracardiac from intracardiac densities. Of greatest importance, is the projection used. In 3 of our 5 cases, filling defects were not seen in the anterior projection but were clearly visualized in the left lateral projection. The left lateral projection is best because only in this projection is the extreme posterior wall of the left atrium visible. It is from this wall that the left atrial mural thrombus arises almost always. The key to the reason for the predilection for this localization of implantation of a left atrial thrombus is present in MacCallum's classic paper[11] of 1924, and cannot be better expressed than in his own words:

> We have found several times a marked thickening of the wall of the left auricle above the base of the more posterior leaflet of the mitral valve. This roughened patch resembles in some degree the vegetations so commonly found there in cases of endo-

carditis produced by the streptococcus viridans, but is evidently more largely produced by a new growth of tissue and to a less extent by the deposition of rough fibrin on the surface. Sometimes the surface, although corrugated, seems not to be roughened by any thrombus mass. . . . In most instances the innermost layer of the auricular wall assumes a hyaline appearance over this whole area and merges gradually into a dense film of fibrin which is exposed to the blood of the auricle.

The cause of the localization of MacCallum's patch is unknown. It may be related to mitral regurgitation, which is so often an integral part of the initial attack of rheumatic carditis, and which is present long before stenosis of the mitral valve sets in. The determining causes for thrombus formation may be the geography of the patch itself, the duration of the rheumatic state and the presence of atrial fibrillation which further slows left atrial circulation time[10] and immobilizes effective atrial contractions. Other explanations have been suggested.[3-6, 12]

Although the left lateral projection is best for visualizing these thrombi, additional projections may be of value, for they may provide supplemental data of the extent of the thrombus.

The diagnosis of thrombus of the left auricle poses a more difficult problem because the left auricle is occasionally not opacified even when it contains no thrombus. Moreover, the opacified left auricle may be obscured in the anterior projection by overlying structures, particularly pulmonary vessels; in the lateral projection it is superimposed upon the anterior superior portion of the left atrium. For the present, therefore, we believe that a diagnosis of left auricular thrombosis should be made only when there is irregular margination of the junction of the auricle with the atrium, together with sparse or no opacification of the auricle. These findings form the basis for our own correct diagnosis of left auricular thrombosis. In our series, however, all were associated with left atrial thrombosis. Read and his associates[13] demonstrated in dogs the angiocardiographic findings of filling defects in the left atrium after invagination of the left auricle.

Radiographically, left atrial thrombi may be confused with tumors. The commonest left atrial tumor is a myxoma.[14] Three left atrial myxomata have been recognized during life by angiocardiography.[9] These tumors are usually of such a size as to produce large filling defects in the left atrium. They are not attached to the posterior wall of the left atrium and produce no filling defects in this region. They are usually attached to the atrial septal wall in the region of the fossa ovalis and this attachment may be visualized.[9] With these points in mind, together with the history and physical findings, the differential diagnosis between myxoma and thrombus appears to be possible.

Summary

1. A diagnosis of thrombosis within the left atrium is possible by angiocardiography.

2. The angiocardiographic diagnosis of a mural thrombus within the left atrium is based upon the finding of a filling defect and irregular margination of the posterior wall of the left atrium best visualized in the left lateral projection.

3. A ball valve thrombus is suggested by the finding of a filling defect within the left atrium unattached to the left atrial wall and small compared to a myxoma.

4. Left auricular thrombosis is suggested by the finding of irregular margination of the junction of the left auricle with the left atrium and sparse or no visualization of the left auricle.

Acknowledgment

We are very grateful to Dr. W. Edward Chamberlain, Chief of the Department of Radiology, Temple University School of Medicine and Hospital, for the privilege of using the facilities of his department.

Summario in Interlingua

1. Le diagnose de thrombose sinistro-atrial per medios angiocardiographic es possibile.

2. Le diagnose angiocardiographic de un thrombo parietal intra le atrio sinistre es indicate post le constatation de un defecto plenatori e de un margination irregular del pariete posterior sinistro-atrial que se visualisa le melio in un projection sinistro-lateral.

3. Le diagnose angiocardiographic de un

globular thrombo valvular es indicate post le constatation de un defecto plenatori intra le atrio sinistre, non attachate al pariete sinistro-atrial e de parve dimensiones in comparation con un myxoma.

4. Le diagnose de thrombose sinistro-auricular es indicate post le constatation de margination irregular del junction del auriculo sinistre con le atrio sinistre e reducite o absente visualisation del auriculo sinistre.

REFERENCES

[1] Scholz, T.: Röntgenologische Darstellung von Herz thromben. Fortschr. Geb. Röntgenstr. **32:** 416, 1924.

[2] Soloff, L. A., and Zatuchni, J.: Unpublished Temple University Hospital Case.

[3] Graef, I., Berger, A. R., Bunim, J. J., and De la Chapelle, C. E.: Auricular thrombosis in rheumatic heart disease. Arch. Path. **24:** 344, 1937.

[4] Jordan, R. A., Scheifley, C. H., and Ewards, J. E.: Mural thrombosis and arterial embolism in mitral stenosis. A clinicopathological study of fifty-one cases. Circulation **3:** 363, 1951.

[5] McGoon, D. C., and Henly, W. S.: The significance of auricular fibrillation and auricular thrombosis in mitral valve surgery. Bull. Johns Hopkins Hosp. **91:** 419, 1952.

[6] Wallach, J. B., Lukash, L., and Angrist, A. A.: An interpretation of the incidence of mural thrombi in the left auricle and appendage with particular reference to mitral commissurotomy. Am. Heart J. **45:** 252, 1953.

[7] Soloff, L. A., Zatuchni, J., and Fisher, H.: Use of planigraphy in demonstration of calcification of heart valves and its significance. Arch Int. Med. **95:** 219, 1955.

[8] Arendt, J., and Cardon, L.: The diagnosis of intraauricular thrombosis in the living. Radiology **53:** 371, 1949.

[9] Goldberg, H., and Steinberg, I.: Primary tumors of the heart. Circulation **11:** 963, 1955.

[10] Soloff, L. A., Zatuchni, J., Stauffer, H. M., and Kelly, E. W.: Angiocardiographic observations of intracardiac flow in the normal and in mitral stenosis. Circulation **13:** 334, 1956.

[11] MacCallum, W. G.: Rheumatic lesions of the left auricle of the heart. Bull. Johns Hopkins Hosp. **35:** 329, 1924.

[12] Wallach, J. B., Lukash, L., and Angrist, A. A.: The mechanism of formation of left auricular mural thrombi. Am. J. Med. **16:** 543, 1954.

[13] Read, J. L., Bosher, L. H., Ferraru, F., Richman, S., and Porter, R. R.: Angiocardiographic demonstration of occlusive auricular thrombi in dogs. Circulation **12:** 247, 1955.

[14] Prichard, R. W.: Tumors of the heart. Review of the subject and report of one hundred and fifty cases. Arch. Path. **51:** 98, 1951.

Hellman, E.: Auricular Fibrillation Following Prolonged Use of Thyroid Extract. J. A. M. A. **159:** 25 (Sept. 3), 1955.

Thyroid is administered in large quantities, in most cases unnecessarily, to patients all over the world. In most cases no great harm results from such medication. Because atrial fibrillation is seldom noted after prolonged administration of large doses of thyroid, the authors report a case in which a patient with normal size heart was noted to have atrial fibrillation and a grade 2 systolic murmur at the apex, together with pitting edema of both legs after taking 3 grains of thyroid daily for 6 years. With omission of thyroid substance, edema diminished progressively and disappeared within 2 weeks. The systolic murmur disappeared in a month's time and previously noted atrial fibrillation was replaced by normal sinus rhythm. Only 3 cases of atrial fibrillation and one case of atrial flutter have been reported arising after thyroid administration to the euthyroid subject; each reverted to regular sinus rhythm following cessation of the use of thyroid.

Kitchell

Emetine Toxicity with Electrocardiographic Abnormalities

By Leslie J. Cera, M.D., M.Sc., F.R.C.P. (C)

Seven case histories are presented illustrating various aspects of the noxious effects of emetine on the heart. T-wave changes, S-T segment deviations, and partial heart block are demonstrated. A case of frank myocardial infarction in a young man occurring during the administration of emetine is described. Finally, both persistence and lability of emetine-induced changes are illustrated.

TOXIC effects of emetine on the heart have long been recognized and some deaths have been attributed to the use of this drug. Objective evidence of its untoward action on the myocardium has generally been presented in the form of electrocardiographic changes, but there have also been some confirmatory necropsy reports. In spite of the undoubted ill effects of this drug in some cases, the opinion is held that indications for its use still exist and that its toxic actions have been overemphasized. Although excellent cases have been documented, many have suffered from incomplete electrocardiographic investigation and inadequate control observations.

Approximately 50 per cent of patients receiving the usual course of emetine hydrochloride intramuscularly manifest some electrocardiographic abnormality. Most of the changes were transient, but some persisted many months. Klatskin and Friedman[1] found electrocardiographic abnormalities in 49 of 93 patients who received emetine. The changes consisted of prolongation of the P-R interval, decreased amplitude or inversion of T waves, slurring and notching of the QRS, extrasystolic beats, a shifting pacemaker, and nodal rhythm. They also stated that the chest pain associated with emetine toxicity has none of the usual characteristics of coronary pain. Hardgrove and Smith[2] reported a case that they initially considered as myocardial infarction on the basis of precordial pain that was not severe but lasted one hour during rest in bed. They dismissed the possibility of myocardial infarction, however, because changes in the S-T segments, Q waves, leukocytosis, increased sedimentation rate, friction rub, and fever were absent.

Change in S-T segments following emetine therapy have been quite rare; when present, they were usually depressions.[3] In approximately 50 per cent of cases, abnormalities have persisted for two to four months. In other cases changes have not been seen for one to two weeks after cessation of treatment.

Seven cases are reported herewith in which electrocardiographic changes were associated with the administration of emetine hydrochloride. These cases were treated at Deer Lodge Veterans' Hospital from 1946 to 1955. Control and follow-up electrocardiograms were generally available.

Report of Cases

Case 1. A. H. M., a 21 year old man, suffered an attack of dysentery in October 1944 while in Italy. In February 1946 cysts of *Entamoeba histolytica* were found in the stool. An electrocardiogram on February 28, 1946, was normal (fig. 1). Emetine hydrochloride, grain 1 intramuscularly, was given daily from March 2 to March 10, 1946, for a total of 9 grains. On March 4, 1946, abnormal flat T waves were seen in leads I, II, and CF_5. On March 21, 1946, the T waves were flat in lead I, inverted in lead II, and biphasic in CF_2, CF_4, and CF_5. The P-R interval was 0.18 second, QRS 0.07, and the rate was 71/min. On May 7, 1946, and again on November 25, 1949, electrocardiograms were normal.

Case 2. C. D., a 22 year old man, had a normal electrocardiogram on October 17, 1946 (fig. 2). From November 27 to December 4, 1946, emetine, grain 1, was given daily for the treatment of amebiasis. On December 6, 1946, the T was inverted in CF_4 and

From the Deer Lodge Veterans' Hospital, Winnipeg, Manitoba, Canada.

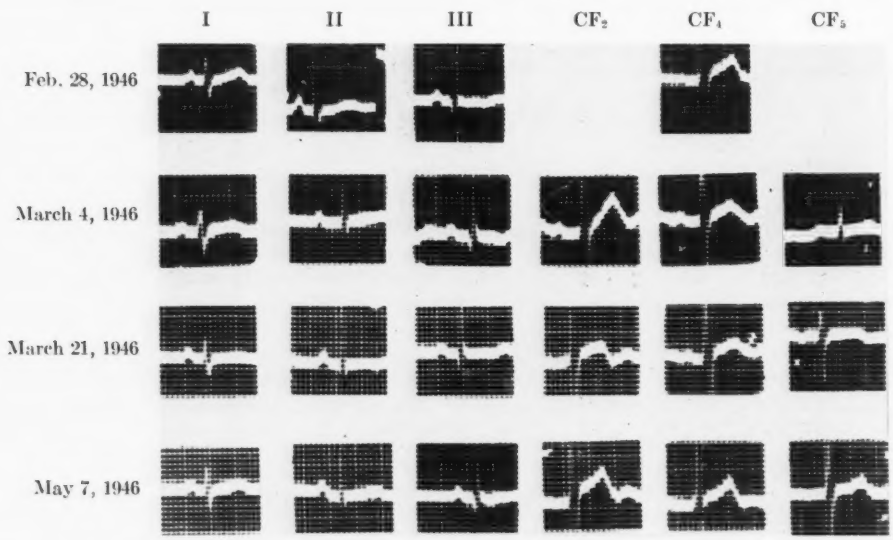


FIG. 1. Case 1, A. H. M. Electrocardiographic complexes.

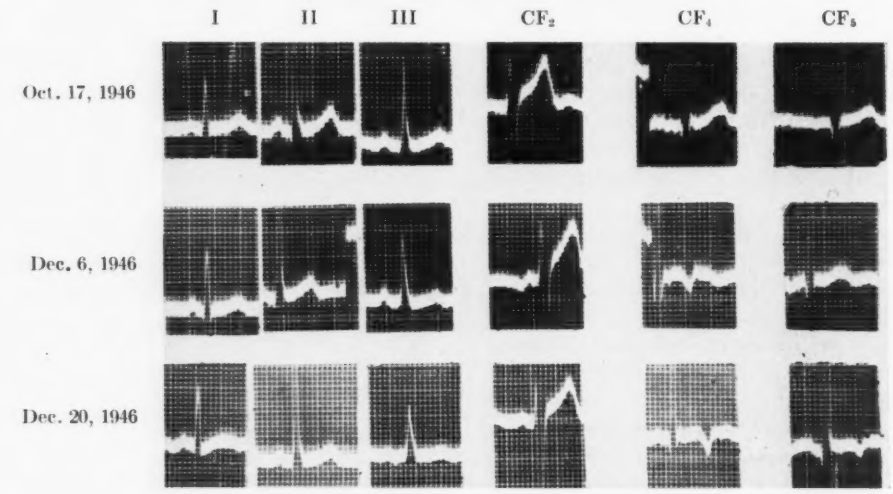


FIG. 2. Case 2, C. D. Electrocardiographic complexes.

ST was elevated with straightening of the ascending limb of the T wave in CF_2. The P-R interval was 0.15 second, QRS 0.07, Q-T interval 0.40, and the rate was 76/min. On December 20, 1946, T waves were flat in lead I and inverted in CF_4 and CF_5, but the ascending limb of T in CF_2 had regained its initial upward concavity.

Case 3. J. O. B., a 22 year old man, suffered with chronic abdominal pain, loose stools, anorexia, and mild nausea during service in Italy from 1943 to 1945. In June 1952, motile amebae and small cysts were found in the stool. On June 20, 1952, an electrocardiogram was normal (fig. 3) and emetine, grain 1 daily, was begun. On June 25, 1952, the T waves were inverted in V_2 and V_4, and flat in V_5 and V_6. The P-R interval was 0.15 second, QRS 0.10, Q-T interval 0.40, and the rate was 73/min. On June 26 emetine was discontinued. On June 27, 1952, T was upright in V_2. On June 30 T was inverted in V_2, V_4, and V_5. The P-R interval was 0.16 second, QRS 0.10, Q-T

0.40, and the rate was 75/min. An electrocardiogram on July 18, 1952, was unchanged, and on August 5, 1952, it was normal.

Case 4. D. L. M., a 28 year old man, was admitted on August 8, 1952, with chills and fever spiking up to 104 F. Malaria due to *Plasmodium vivax* was demonstrated, and motile and cystic forms of *E. histolytica* were found in the stool. On August 14, 1952, an electrocardiogram was normal (fig. 4); emetine hydrochloride, grain 1 intramuscularly, was given daily from August 14 to 21. On August 18 the electrocardiogram was unchanged. On August 22 the T wave was inverted in V_4; the P-R interval was 0.16 second, QRS 0.09, Q-T 0.40, and the rate was 79/min. No follow-up study was obtained.

Case 5. A. K., a 28 year old man, was found to have motile *E. histolytica* in the stool on July 30, 1952. On July 31 an electrocardiogram was normal, with a P-R interval of 0.17 second (fig. 5). Emetine, grain 1 intramuscularly, was given daily from August 1 to 9. On August 9 an electrocardiogram revealed a P-R interval of 0.21 second and a flat T wave in lead I. On November 26, 1952, an electrocardiogram was normal, with a P-R interval of 0.17 second.

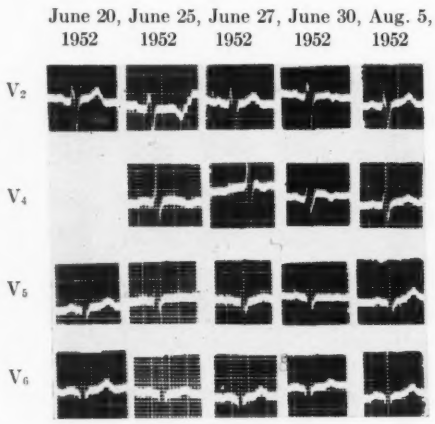


FIG. 3. Case 3, J. O. B., Electrocardiographic complexes.

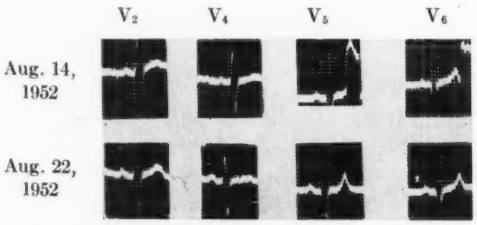


FIG. 4. Case 4, D. L. M. Electrocardiographic complexes.

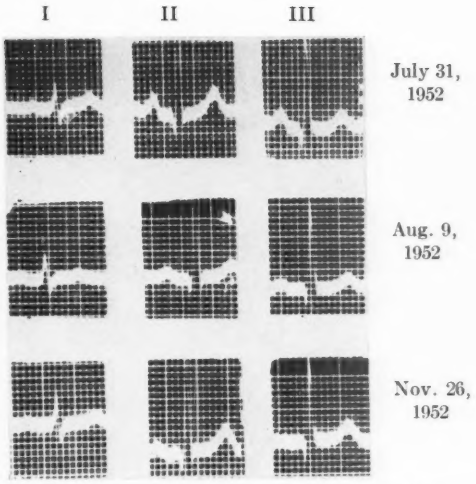


FIG. 5. Case 5, A. K. Electrocardiographic complexes.

Case 6. D. M. S., a 39 year old man, was found to have cysts of *E. histolytica* in the stools on July 15, 1948. On July 16 an electrocardiogram showed a flat T wave in lead I, P-R interval of 0.12 second, QRS 0.07, Q-T interval 0.36, and a rate of 60/min. (fig. 6). Emetine was given in a dose of 1 grain daily from July 19 to 26. On August 14, 1948, the T waves were flat in lead I and inverted in CF_4 and CF_5, the P-R interval was 0.17 second, QRS 0.07, Q-T interval 0.42, and the rate was 67/min. On August 26 the electrocardiogram was back to the pretreatment state and was unchanged in March 1949 and February 1950.

Case 7. H. M. W., a 35 year old man, showed *E. histolytica* in the stool on January 7, 1955. At that time the sedimentation rate was 3 mm. in 1 hour. An electrocardiogram on January 8 was normal (fig. 7). Emetine, grain 1 daily, was given from January 8 to 14. On January 15 T waves were flat in leads I, II, aV_L, aV_F, V_5, and V_6. P-R interval was 0.16 second, QRS 0.08, Q-T 0.38, and the rate was 65 per minute.

On January 17 the patient complained of squeezing retrosternal pain that lasted some hours and was worse on breathing. There were a large Q_3 and S-T elevations in leads II, III, aV_F, and V_{4-6}. The sedimentation rate remained at 3 mm. in 1 hour. On February 8 the abnormalities had increased and were consistent with posterolateral infarction. There was no marked change on March 9. On April 4 the abnormalities were receding, but were still present on April 19. On October 25 the patient had severe stabbing pain deep in the midchest, radiating to the left shoulder, that was provoked by strenuous activity and was relieved after rest for 20 minutes. The sedimentation rate remained at 4 mm. After a period of observation in hospital, a Master step test was

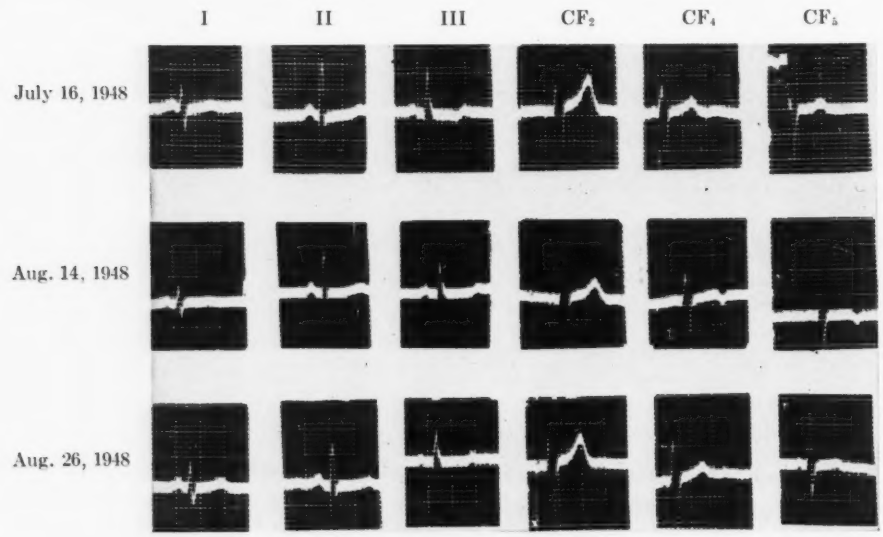


FIG. 6. Case 6, D. M. S. Electrocardiographic complexes.

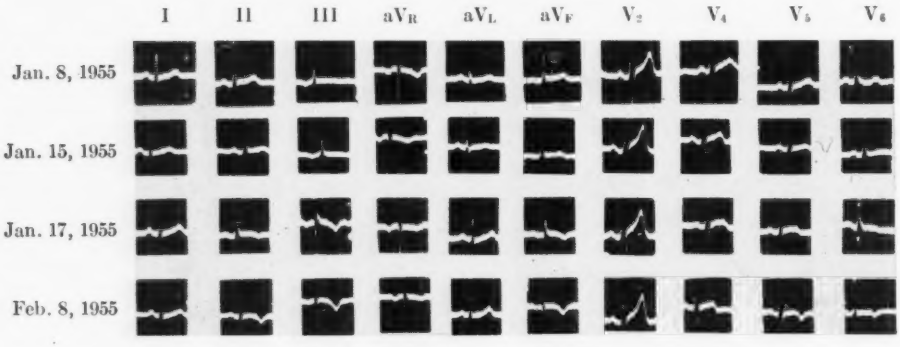


FIG. 7. Case 7, H. M. W. Electrocardiographic complexes

done (fig. 8), which produced a paradoxic elevation of T in lead II and aV_F, and to a lesser extent in V_6. On completion of the exercise, mild retrosternal discomfort was present, which subsided quickly on resting. On November 28 2 bouts of retrosternal pain were provoked by short brisk walks; on both occasions nitroglycerin afforded quick relief.

DISCUSSION

In each of the 7 cases electrocardiographic changes were consequent upon emetine therapy. They included flattening and inversion of T waves, elevation and change in contour of S-T segments, prolongation of atrioventricular conduction time, and frank myocardial infarction. In addition, these changes showed both persistence and lability.

None of the patients had fulminating or severe dysentery, but amebae were discovered in routine investigation of the stools in patients either with mild bowel disturbances or who were known to have been in an endemic area. The possibility that the electrocardiographic changes were secondary to electrolyte disturbances consequent upon marked dysentery may therefore be dismissed. The changes may not be reasonably attributed to amebiasis itself; in 5 of the 7 cases the electrocardiogram was normal before treatment,

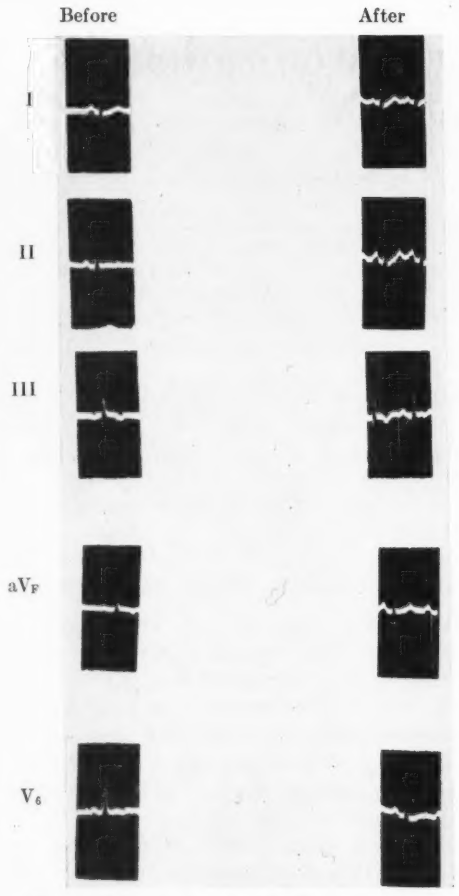


FIG. 8. Case 7, H. M. W. Electrocardiographic complexes before and after two-step exercise tolerance test.

and within days of the institution of emetine injections acute changes were demonstrated without even slight evidence of concomitant flare-up of the chronic disease. The other 2 cases deserve short comment. In case 6, a minor electrocardiographic abnormality was noted prior to emetine administration. Without any change in clinical status after the drug was given, the abnormality progressed significantly, only to revert to pretreatment status on discontinuance of the drug. In the final case, the incriminating evidence is admittedly circumstantial.

It is only possible to speculate about the role of emetine in the production of myocardial infarction. Although it is tempting to attribute this to an esoteric lesion such as coronary arteritis, it is perhaps necessary to accept the explanation that therapy and infarct were spuriously allied in time. The pain and the electrocardiographic changes possibly reflected a large area of myocarditis due to emetine, but in view of the subsequent history of angina pectoris, the diagnosis of coronary artery disease seems more reasonable.

Finally, from the very limited postmortem material in the literature, the underlying lesion in the majority of cases would appear to be an interstitial myocarditis of toxic rather than inflammatory origin.[4]

SUMMARY

Data from 7 cases demonstrate electrocardiographic changes following the administration of emetine hydrochloride.

The history of a young patient who sustained myocardial infarction while receiving emetine has been presented.

SUMMARIO IN INTERLINGUA

Datos ab 7 casos demonstra alterationes electrocardiographic post le administration de hydrochlorido de emetina.

Es presentate le historia clinic de un juvene patiente qui suffreva infarcimento myocardial durante un curso de emetina.

ACKNOWLEDGMENT

I am indebted to Dr. L. R. Coke, Cardiologist to Deer Lodge Veterans' Hospital, for suggesting this study.

REFERENCES

[1] KLATSKIN, G., AND FRIEDMAN, H.: Emetine toxicity in man. Ann. Int. Med. **28:** 892, 1948.

[2] HARDGROVE, M., AND SMITH, E. R.: Effects of emetine on the electrocardiogram. Am. Heart J. **28:** 752, 1944.

[3] DACK, S., AND MOLOSHOK, R. E.: Cardiac manifestations of toxic action of emetine hydrochloride in amebic dysentery. Arch. Int. Med. **79:** 228, 1947.

[4] BREM, T. H., AND KONWALER, B. E.: Fatal myocarditis due to emetine hydrochloride. Am. Heart J. **50:** 476, 1955.

Atrioventricular Synchronization and Accrochage

By HENRY J. L. MARRIOTT, M.A., B.M. (OXON.)

Complete heart block implies an absolute independence between atria and ventricles that does not in fact always exist. Segers showed that, after complete block was artificially produced in the frog's heart, atria and ventricles would sometimes begin to beat exactly in phase, most commonly in a 2 to 1 ratio. He subsequently reported one clinical example of 2 to 1 A-V synchronization in a patient with complete heart block. Two further cases that may illustrate different varieties of synchronization are here presented.

ATRIOVENTRICULAR synchronization has received scant attention in the English literature. The purpose of this communication is to re-emphasize this phenomenon and to present electrocardiographic records that may represent clinical examples of it.

DEFINITION OF TERMS

When separate and distinct cellular elements, having no anatomic continuity and possessing inherently different rhythms, are placed in contact with each other, they sometimes begin to discharge impulses simultaneously at a common rate; when this occurs, it is logically called *synchronization*. Such synchronization has long been known to occur in juxtaposed nervous tissues; it has also been shown to develop in fragments of heart muscle or in whole cardiac chambers placed in contact; and when complete block is present, it may develop in the living heart between atria and ventricles.

If the "hook-up" between cardiac elements is short-lived, lasting for only a few beats, after which the separate elements resume their former independent rhythms, Segers[1] has applied the term *accrochage* (a hooking together). Thus there is overlap between the two terms, accrochage being merely a brief bout of synchronization.

It may here be emphasized that atrioventricular synchronization does not mean merely the synchronous or almost synchronous contraction of atria and ventricles—else the definition would embrace A-V nodal rhythm. The essence of synchronization is that atria and ventricles respond to their own separate pacemakers which are, however, beating synchronously—two individuals retain their separate autonomy, yet walk for a while in step.

REVIEW OF LITERATURE

(1) *Synchronization between Cardiac Fragments*

In 1946 Segers[1] reported that if two fragments of frog heart were placed in contact, they would often begin to contract exactly in phase. He found that for this to occur the rates of the 2 fragments must not differ by more than 25 per cent: the incidence of synchronization was indeed proportional to the difference in rates—at a 25 per cent difference it became a rare phenomenon, whereas when rates were within 1 or 2 per cent of each other, prolonged synchronization developed in approximately half his experiments. The rate at which the two fragments "synchronized" was equal to, or more often slightly less than, that of the more rapidly beating fragment; thus synchronization was primarily the result of an acceleration of the more slowly beating fragment with minor if any slowing of the more rapid fragment.

Synchronization was also observed to occur in a 2 to 1 ratio, especially when an atrial fragment was placed in contact with a ventricular fragment. This 2 to 1 type of synchronization occurred in more than half the experiments when the inherent rate of the ventricular fragment was between 45 and 53 per cent of the rate of the atrial fragment. More rarely 3 to

1, 4 to 1, or even 3 to 2 ratios were observed. The 3 to 2 type of synchronization, in which every third systole of the more rapid rhythm coincides with every second systole of the slower, is clearly a more complex interrelationship than the others, as it involves systoles in both fragments that are "out of phase." Attention is drawn to it because the second record here presented (fig. 5) may represent a clinical example of a similarly complex interreaction between atria and ventricles.

In Segers[1] experiments synchronization, when it occurred, lasted variously from a few seconds (accrochage) to 10 minutes or more. That it was due to the synchronous discharge of the same two previously independent pacemakers was clear from the fact that the action currents from each fragment remained unchanged in form.

(2) *Atrioventricular Synchronization in Experimental Heart Block*

Many years ago Erlanger and Blackman[2] in the dog's heart and Demoor and Rijlant[3] in the rabbit's had shown that artificially created complete atrioventricular block was sometimes associated with periods of what we may now call sychronization between atria and ventricles. Their records were entirely mechanical, however, and therefore gave no indication of the electric mechanism of the synchronous discharge. From their data it was entirely possible that atria and ventricles were under the control of a single intermediate pacemaker rather than responding to two separate but synchronized pacemakers.

Segers[1] was able to produce periods of synchronization or accrochage in the frog's heart in which he had produced complete block by destroying the conducting tissues. The usual A-V ratio obtained was 2 to 1, but at times 1 to 1 or 3 to 1 synchronization developed. This led him and his colleagues to explore the possibility that similar interreactions between atria and ventricles might occur in patients with complete A-V block.

(3) *Clinical Atrioventricular Synchronization*

In 1929 van Buchem[4] commented "atria and ventricles frequently do not function so independently in complete heart block as one might be inclined to think." He described a patient with complete A-V block in whom the intrinsic atrial rate was slower than that of the ventricles; whenever the P wave, having "overtaken" and passed the QRS complex, reached a distance of 0.19 second after the onset of the QRS, then the rate of the atria accelerated to become identical with that of the ventricles. This observation was not documented with a published tracing. Subsequently, Fischer[5] and Kisch[6] also stated, but again without publishing illustrative tracings, that the rhythms of atrial and ventricular pacemakers could synchronize during complete A-V block.

In 1947 Segers[7] described a patient with complete block whose atrial rate was constantly double that of the ventricles. That this was not simply a 2 to 1 A-V block was clear from the facts: (1) the P waves varied in their relationship to the QRS complexes—sometimes appearing before, sometimes after, and sometimes coinciding with them—but always remained closely "hooked" to them; (2) exercise increased the atrial rate without appreciably influencing that of the ventricles.

The following cases illustrate two further possible forms of atrioventricular synchronization:

Case 1. A white male of 66 years was admitted to the hospital on December 27, 1954. He had enjoyed good health until 4 weeks before admission. At that time he developed a respiratory infection that was followed by progressive shortness of breath and chest pain. On admission he was cyanotic and dyspneic. The heart was regular at a rate of 130 and the blood pressure was 140/80. Rales were heard over both lung fields; the liver was not felt, and there was no edema. Blood urea was elevated and x-ray films of chest showed massive cardiac enlargement. A respiratory acidosis was reflected in carbon dioxide combining powers of 76 and 79 volumes per cent.

At first there was some response to measures directed at the congestive heart failure and pulmonary edema but on the seventeenth hospital day the patient suffered a cerebral accident with right hemiplegia. Two days later acute pulmonary edema developed but responded to treatment. Five days after this, on the twenty-fourth hospital day, another attack of pulmonary edema occurred. Once again the patient was rescued but after this he progressively deteriorated and died on Feb. 4, 1955.

Digitalis was administered as follows: during the

first three days in the hospital he received a total of 1.6 mg. of Cedilanid intramuscularly. During the next 14 days 0.2 mg. of Cedilanid was injected daily except on 2 days when a double dose was given. Oral gitalin was then administered for a further 16 days in a daily dose of 0.5 mg. except on 3 days when this dose was doubled. Thus, at the time of the tracing shown in figure 2, he had received in 33 days a total of 4.8 mg. of Cedilanid by intramuscular injection and 9.5 mg. of gitalin by mouth. Quinidine 0.2 Gm. every 6 hours was administered throughout most of the hospital course.

The salient features of serial electrocardiograms were as follows: 12/30/54: S-A tachycardia at 136 with nonspecific ST-T abnormalities; 1/20/55: Normal sinus rhythm with incomplete A-V block; 1/28/55: See figure 2 (discussed in detail below); 2/3/55: S-A tachycardia with complete A-V block; atrial rate 155, ventricular rate 120.

At autopsy the heart weighed 425 Gm. The left ventricle was dilated and its wall thickened. There was no gross evidence of coronary artery occlusion or of myocardial infarction. Microscopically, however, there were focal areas of fibrous tissue replacement in the wall of the left ventricle secondary to sclerotic changes in the arterioles. Sections taken from the septum in the region of the conducting tissues showed inflammatory cells, new vessel formation, and focal areas of fibrous tissue; these were considered to be evidence of a recent infarction, probably less than a month old.

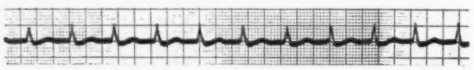


FIG. 1. Strip of lead I with normal QRS duration and absent P waves suggesting "mid-nodal" tachycardia; but normal P waves emerge later from under cover of QRS complexes (lead I, fig. 2).

The pattern observed in figures 1 and 2 would seem to admit of three conceivable interpretations. To dismiss the least acceptable first, since P waves in lead I were clearly visible in previous tracings and the QRST configuration was unchanged, a strip of lead I such as that shown in figure 1 would un-

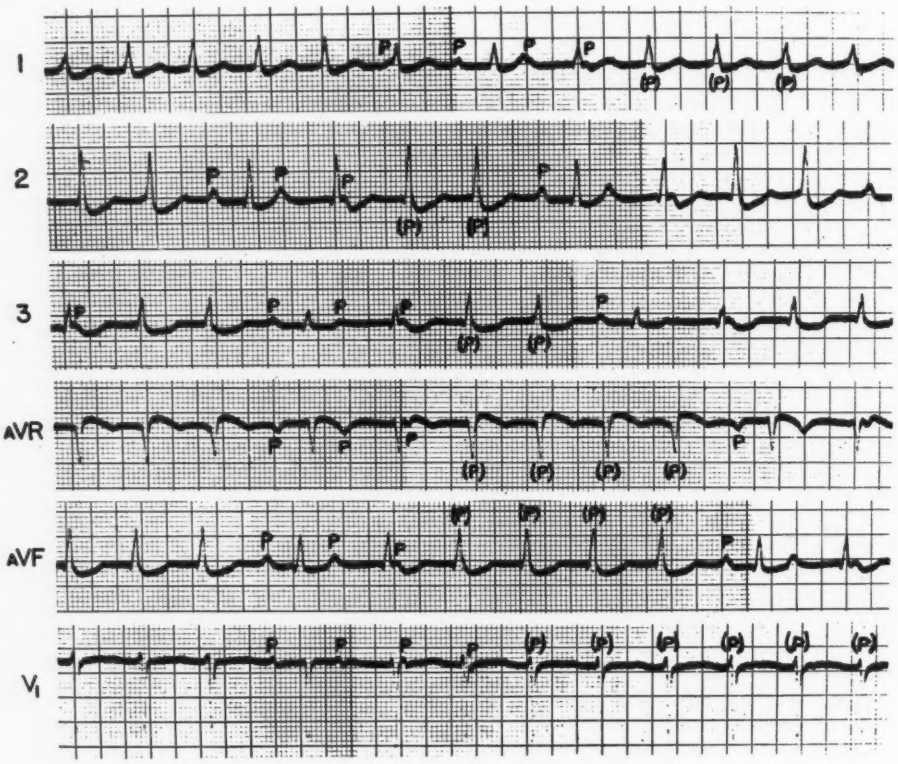


FIG. 2. For detailed description, see text

doubtedly be interpreted as A-V nodal tachycardia of "mid-nodal" type. That this is probably not the mechanism becomes apparent when one sees P waves of *sinus* form emerging from time to time in what appear to be short runs of progressively increasing incomplete A-V block or of complete A-V block (fig. 2). It still remains a bare possibility that short bouts of sinus rhythm with A-V block alternate with runs of nodal tachycardia. This is rendered highly improbable, if not impossible, by the observed facts: (1) the ventricular rate, as soon as the P waves begin to coincide with the QRS complexes, becomes identical with the atrial rate as observed in the short stretches where P waves are visible, suggesting that the ventricles are now under atrial control. It is an almost inconceivable coincidence that, at the precise moment when the next sinus impulse is due, the A-V node should abruptly assume control at a rate identical with that of the S-A node; (2) that P waves of normal *sinus* form are seen partially submerged in the QRS complex, at the beginning (leads I, II and V1) and at the end (lead I) of the runs of supposed "nodal" rhythm. Moreover, it will be noted that in all the leads (except V1 where P is biphasic) the QRS complexes containing buried P waves are of greater amplitude than those situated between visible P waves. This suggests that the buried P waves add height (or depth in aV_R) to the QRS complexes and, therefore, must be of the same polarity as the QRS. In every instance this polarity is consistent with normal sinus P waves rather than with waves of A-V nodal form.

Two more plausible possibilities suggest themselves, both of which invoke the mechanism of synchronization. One of these is that after short runs of independent rhythm, the atria and ventricles begin to synchronize. From the short runs of supposedly independent rhythm one sees that the ventricular rate is about 85 and the atrial rate 115. When synchronization occurs, as in Segers'[1] experiments, the more slowly beating element accelerates to keep pace with the faster. If a diagram be made in Segers' mode, the A-V relationships supposed can be graphically shown as in figure 3.

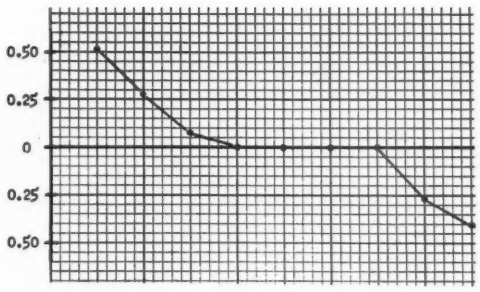


FIG. 3. A-V relationships plotted (on the assumption of complete A-V block) from lead aV_F, figure 2. The zero line represents the incidence of P waves and the black dots represent QRS complexes. Points plotted above the zero line thus represent successive "R-P intervals" (beginning with that of the first labeled P wave) before synchronization occurs; the fourth to the seventh beats represent synchronized P waves and QRS complexes; points plotted below the line represent succeeding "P-R intervals."

Against the argument for complete block with idioventricular rhythm is the fact that the ventricular rhythm, during the periods where P waves are apparent, is not regular; there is a progressive shortening of the R-R interval. Furthermore, if we accept complete A-V block, two obvious differences from the usual behavior of Segers'[1] synchronizing tissues present themselves and perhaps deserve comment: (1) the intrinsic rhythms of the two pacemakers are rather widely separated, the ventricular rate (85) being only 74 per cent of the atrial (115); (2) during the periods of accrochage, synchronization is achieved exclusively through acceleration of the ventricles with no retarding of the atria.

The remaining and most attractive possibility is that the record shows only incomplete A-V block with P-R intervals progressively lengthening until synchronization occurs. Beginning with the first labeled P wave in lead aV_F (fig. 2) we may measure successive P-R intervals as 0.26, 0.42, and 0.50 second. The next P wave is then lost in the QRS complex and the P-R interval is, therefore, equal to the R-R interval (0.54 sec.). For the next few beats the P-R interval remains equal to the

FIG. 4. A-V relationships plotted (on the assumption of incomplete A-V block) from lead aV_F, figure 2. Beginning with the first labeled P wave, progressively longer P-R intervals are represented until the QRS of the preceding cycle synchronizes with the next P wave; they then remain so synchronized until a ventricular beat is dropped.

R-R interval, so that the P wave "belonging" to the next QRS complex remains concealed in the preceding QRS. If this is the correct interpretation, it represents synchronization of the atrial impulse with the ventricular impulse of the *preceding* cardiac cycle and the A-V relationships may be represented as in figure 4. If this explanation is acceptable, it is necessary to assume that the P-R interval occasionally exceeds the R-R interval. Thus the QRS immediately following the first labeled P wave in lead I (fig. 2) must represent the ventricular response to the P wave buried in the preceding QRS complex.

Case 2. A 49-year-old white man had his first known attack of rheumatic fever at the age of 38. At that time his physician told him that he must have had rheumatic heart disease for many years. For the past 10 years he has had mild exertional dyspnea. Three years ago the electrocardiogram showed right bundle branch block. One week before the tracing here presented (fig. 5) he "nearly fainted" at work—he felt weak, his heart pounded, and he became noticeably pale. During the next few days he had rather frequent spells of similar type; he lost consciousness in none of them. Since the time of this tracing, spells have become infrequent and a subsequent electrocardiogram has shown constant complete A-V block.

The tracing in figure 5 is included solely because it may represent the clinical counterpart of the unusual form of 3 to 2 synchronization observed by Segers in his animal experiments. In the tracing sinus rhythm at a rate of about 85 with incomplete A-V block alternates with complete block and idioventricular rhythm at a rate of about 58. The periods of sinus rhythm are associated with right bundle branch block, the pattern of which is identical with that

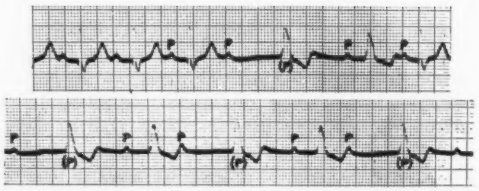


FIG. 5. Runs of sinus rhythm with incomplete A-V block and right bundle branch block alternating with complete A-V block and idioventricular rhythm. The sequence shown was repeated again and again. The bouts of idioventricular rhythm always began after a dropped beat and the first idioventricular complex always exactly coincided with the time of the next expected P wave. During the runs of idioventricular rhythm a constant P to QRS ratio of 3 to 2 was observed—every third P wave synchronized with every other QRS complex.

constantly observed in the record a year previously. In the 12 lead electrocardiogram from which figure 5 is taken, the mechanisms rapidly alternated—the longest run of sinus rhythm observed being 16 beats and the longest of idioventricular rhythm, 15 beats. Each run of idioventricular rhythm began with an idioventricular QRS complex which coincided exactly with the expected time of the next P wave.

A "ventriculo-atrial" arrhythmia, of the type to which attention was first drawn by Erlanger and Blackman[2] in 1910 and which has been the subject of many observations and discussions since, was also to be seen in the tracing during the bouts of complete block with idioventricular rhythm. This is clearly discernible in the strip reproduced in figure 5—the P-P intervals containing ventricular complexes are shorter than the non-QRS-containing P-P intervals.

Mechanism of Synchronization

When independent cardiac fragments or chambers are placed in contact, it is obviously possible that the influences mutually exerted may be either mechanical or electric or both. Segers[1] showed that the phenomenon could be mediated by electric influences alone; for he found that synchronization developed in heart fragments that were mechanically isolated and were connected only by a "bridge"

of electrolytes (Ringer's solution). But he also demonstrated that mechanical stimuli alone could induce synchronization; for he showed that, if two isolated ventricles were fixed on the 2 branches of an inverted Y-shaped cannula filled with a nonconducting medium (liquid paraffin), so that the contraction of either ventricle would displace paraffin into the other, thus raising the pressure within it, synchronization not infrequently developed.

Whether mechanical or electric stimuli play the decisive role in establishing atrioventricular synchronization in the presence of complete block remains to be determined; at present one can only speculate. What seems clear is that, in the presence of complete A-V block, all degrees of independence between atria and ventricles can exist. At one end of the scale is the classic concept of complete independence with each moiety beating regularly and being entirely uninfluenced by the other. At the other end of the scale comes prolonged atrioventricular synchronization. In between are shorter and less stable periods of synchronization (accrochage); and minor and often transient disturbances of one another's rhythm, such as the ventriculo-atrial arrhythmia mentioned above the mechanism of which has remained a subject of hot dispute for decades.

Summary

1. The subject of synchronization (and accrochage) between independent cardiac elements is reviewed.

2. An example of A-V block, with short periods of presumable synchronization between atria and ventricles in a patient with recent myocardial infarction involving the septum, is presented. Possible interpretations of the electrocardiogram are discussed in detail.

3. A second patient with rheumatic heart disease, who has recently developed complete A-V block, presents a 3 to 2 A-V ratio that may represent a complex form of synchronization.

4. The mechanism of synchronization is briefly discussed.

Summario in Interlingua

1. Le thema del synchronisation (e accrochage) inter independente elementos cardiac es passate in revista.

2. Es presentate un exemplo de bloco atrioventricular, con breve periodos de synchronisation (probabile), occurrente in un patiente con recente infarcimento myocardial afficiente le septo. Interpretationes possibile del electrocardiogramma es discutite in detailio.

3. Un secunde patiente con morbo cardiac rheumatic, qui disveloppava recentemente un complete bloco atrio-ventricular, presenta un proportion atrio-ventricular de 3.2 que forsan corresponde a un complexe forma de synchronisation.

4. Le mechanismo de synchronisation es discutite brevemente.

Acknowledgment

I am indebted to Dr. J. Sheldon Eastland for permission to report case 1 and to Dr. C. Gardner Warner for his careful interpretation of the pathologic findings; to Dr. Henry J. Klaunberg for providing me with an expert translation of Segers' key article; and to Dr. A. F. Schubart for his indispensable help in translating the German papers.

REFERENCES

[1] Segers, M.: Les phénomènes de synchronisation au niveau du coeur. Arch. internat. de physiol. **54:** 87, 1946.

[2] Erlanger, J., and Blackman, J. R.: Further studies in the physiology of heart block in mammals; chronic auriculo-ventricular heart block in the dog. Heart **1:** 177, 1910.

[3] Demoor, J., and Rijlant, P.: Contributions à la physiologie générale du coeur. IX. Le mécanisme du travail des ventricules. Arch. internat. de physiol. **27:** 397, 1926.

[4] van Buchem, F. S. P.: Dissoziation zwischen Atrium und Ventrikel. Erklärung des partiellen Herzblocks. Ztschr. klin. Med. **110:** 401, 1929.

[5] Fischer, R.: Über das Vorkommen einfacher zahlenmässiger Beziehungen zwischen der Frequenz dissoziiert schlagender Herzabschnitte. Ztschr. klin. Med. **116:** 466, 1931.

[6] Kisch, B.: Beobachtungen bei einem Kranken mit totalem Block. Cardiologia **2:** 47, 1938.

[7] Segers, M., Lequime, J., and Denolin, H.: Synchronisation of auricular and ventricular beats during complete heart block. Am. Heart J. **33:** 685, 1947.

Comparison of Large and Small Doses of Hormones in the Treatment of Acute Rheumatic Carditis

By SUJOY B. ROY, M.B., M.R.C.P., D.T.M.&H. (EDIN.), AND BENEDICT F. MASSELL, M.D.

Disappearance of significant murmurs was twice as common in 47 rheumatic children treated with large doses of hormones as in a comparable group of 41 children treated with small doses of hormones. Results were also related to the duration of illness before therapy was started. The findings suggest that the divergencies of opinion regarding the efficacy of hormones in the treatment of acute rheumatic carditis may in part be explained on the basis of differences in doses of hormones, in duration of therapy, and in duration of illness before the beginning of therapy.

IN THE last 6 years, ever since Hench and his associates[1] first pointed out the apparent usefulness of corticotrophin (ACTH) and cortisone in the treatment of rheumatic fever and rheumatic carditis, various investigators, both from this country and abroad, have expressed divergent opinions on the efficacy of these hormones in the treatment of rheumatic fever. The opinions range from those of the ultraoptimistic group, who believe hormones terminate the disease, to those of the over pessimistic group, who are convinced that hormones are in no way a better suppressive drug than aspirin.[2] The report of a cooperative clinical trial,[3] which has recently been published simultaneously in this country and in the United Kingdom, indicated that there was no consistent pattern in the response of the various manifestations of rheumatic fever in patients treated for 6 weeks with ACTH, cortisone, or aspirin, and that "no consistent difference in the behavior of murmurs present at the start of treatment was noted except that the soft apical systolic murmurs disappeared more rapidly in hormone treated groups." This clinical trial, usually referred to as the Cooperative Study, was a study in which 6 centers in the United Kingdom, 1 in Canada, and 5, including the House of the Good Samaritan, in the United States participated.

The divergencies of opinion regarding the relative efficacy of hormones in the treatment of rheumatic fever and rheumatic carditis led us to consider whether these differences could be explained, in part, on the basis of differences in dosage, in duration of therapy, and in duration of illness before starting therapy. The purpose of the study being reported here was to explore these possibilities. Heart damage being the most important effect of rheumatic fever, the results of hormone therapy in this study have been evaluated regarding data pertaining to carditis only. Furthermore, since carditis is best indicated by the presence of significant murmurs, this study has been confined to observations of the frequency with which murmurs present at the start of the treatment disappeared completely at the end of the twentieth week from the beginning of therapy.

It should be noted that the present study is not concerned with the relative merits of hormones and salicylates in the treatment of rheumatic fever nor with the toxic and other undesirable effects of these drugs.

SUBJECTS

At the House of the Good Samaritan, Boston, between May 1949 and December 1954, a total of 160 rheumatic fever patients under the age of 17 years were treated with variable doses of ACTH and cortisone for varying lengths of time. Of these patients, 88 who were in their initial attack of rheumatic fever and who presented definite signs of carditis, in addition to other signs of active rheu-

From the House of the Good Samaritan, Children's Medical Center and the Department of Pediatrics, Harvard Medical School, Boston, Mass.

This study was supported by a research grant (HG-956) from the National Heart Institute, U.S. Public Health Service; and by a fellowship grant from the Massachusetts Heart Association.

TABLE 1.—*Frequency of Rheumatic Fever Manifestations in Patients with Carditis*

	Small-Dose Group (41 Patients)	Large-Dose Group (47 Patients)
	%	%
Significant murmurs	100	100
Cardiac enlargement	34	34
Pericarditis	22	15
Congestive failure	24	21
Nodules	27	38
Joint pains	85	82
Erythema marginatum	24	17
Elevated sedimentation rate	98	94
Antistreptolysin-0 titer of 400 units or more	95	100
Prolonged P-R interval	22	23

matic fever prior to therapy, were selected for this study. Carditis was not considered to be present unless there were significant murmurs.

All of the patients with significant murmurs in this study had signs of mitral regurgitation or signs of aortic regurgitation. There were no instances of aortic stenosis or mitral stenosis. Mitral regurgitation was diagnosed on the basis of a long, blowing systolic murmur that was best heard at the apex, was of more than slight (grade II) intensity at the apex, radiated to the left axilla, and did not change appreciably with respiration or with change in the patient's position. In some instances, this significant systolic murmur was accompanied by a rumbling mid-diastolic murmur at the apex. Aortic regurgitation was diagnosed on the basis of an early diastolic blowing murmur which, even when faint, occupied more than half of diastole.

Of the 88 patients with significant murmurs prior to therapy, 41 were treated with relatively small doses of the hormones for an average of 6 weeks and 47 were treated with relatively large doses of the hormones for an average of 14 weeks. Those in the small-dose group were given intramuscularly a total of 1100 to 2400 units of lyophilized ACTH* or 4.1 Gm. of cortisone.† Those in the large-dose group were given a total of 4100 to 7000 units of ACTH-gel intramuscularly or 13.0 to 15.5 Gm. of cortisone orally.

* All the ACTH used in this study was donated by the Armour Laboratories. The kind that was used in the small-dose group was a water-soluble lyophilized preparation standardized in terms of USP units. The USP unit is expressed as a milligram equivalent of ACTH lot number LA-IA. That used in the large-dose group was a purified long-acting preparation in a gelatin base supplied as H. P. Acthar gel and standardized in terms of Armour units.

† All cortisone used in the study was Cortone Acetate and was donated by Merck and Co.

TABLE 2.—*Frequency of Complete Disappearance of all Significant Murmurs Twenty Weeks after Beginning of Therapy*

Interval in days between onset of rheumatic fever and beginning of therapy	Small-Dose Group			Large-Dose Group		
	Cases with significant murmurs	Disappearance of murmurs		Cases with significant murmurs	Disappearance of murmurs	
		Number	Per cent		Number	Per cent
1 to 7	6	3	50	11	8	73
8 to 14	12	3	25	7	3	43
15 to 42	15	2	13	15	6	40
More than 42	8	0	0	14	2	14
Total cases	41	8	20	47	19	40

All of the patients in the small-dose group were treated prior to July 1952; all of the patients in the large-dose group were treated after that date.

The frequency of important clinical and laboratory signs of rheumatic fever and carditis in the 41 cases of the small-dose group is compared in table 1 with the frequency in the 47 cases of the large-dose group. Such manifestations as cardiac enlargement, joint symptoms, elevation of the sedimentation rate, elevation of the antistreptolysin-O titer, and prolongation of the P-R interval occurred with almost exactly the same frequency in the 2 groups. The incidence of pericarditis and congestive failure was slightly greater in the small-dose group, but the incidence of subcutaneous nodules and chorea was somewhat greater in the large-dose group.

RESULTS AND DISCUSSION

The 41 patients in the small-dose group and the 47 patients in the large-dose group were divided into subgroups according to the interval that elapsed between the onset of the rheumatic fever attack and the beginning of hormone therapy. The frequency with which all significant murmurs had completely disappeared by the twentieth week from the beginning of therapy for each sub-group is shown in table 2.

From the data in the table it is evident that, in both the small and the large-dose groups, the shorter the duration of illness prior to the start of therapy, the greater the frequency of complete disappearance of all significant murmurs. Thus, in the small-dose group the frequency of disappearance of murmurs decreased from 50 per cent for patients ill 1 to 7 days to 0 per cent for patients ill more than 42 days, and in the

large-dose group the frequency for the corresponding subgroups decreased from 73 per cent to 14 per cent.

It is also to be noted that in each duration subgroup, the frequency of complete disappearance of all significant murmurs in the large-dose group was consistently greater than the frequency in the small-dose group. Thus, for the 4 successive duration subgroups the percentages of disappearance of significant murmurs in the large-dose and the small-dose groups were respectively 73 and 50; 43 and 25; 40 and 13; and 14 and nil. For all patients, irrespective of duration of illness, the frequency of disappearance of significant murmurs was 40 per cent for the large-dose group and only 20 per cent for the small-dose group, a ratio of 2 to 1.

Statistical analysis reveals the following: in the large-dose group the difference in frequency of disappearance of murmurs in patients treated within 7 days of onset of rheumatic fever and in patients treated after an elapse of more than 42 days is significant, in that p is almost .01; the frequency of disappearance of murmurs in all of the patients in the large-dose group treated within 42 days of onset (17 out of 33 cases) is significantly greater than the frequency in those treated after an elapse of more than 42 days (2 out of 14 cases), in that p is approximately .02; of all the patients treated within 42 days of onset of rheumatic fever (66 cases) the frequency of disappearance of murmurs is significantly greater in the large-dose group (17 out of 33 cases) than in the small-dose group (8 out of 33 cases), in that p is approximately .02.

It is to be noted that the patients in the small-dose and large-dose groups were not treated concurrently. Furthermore, the number of cases in each duration subgroup is relatively small. Hence, we hesitate to attach great weight to statistical evaluation. Nevertheless, the consistent difference between the small-dose and the large-dose groups in regard to frequency of disappearance of murmurs within each duration subgroup is impressive. Furthermore, the relation of frequency of disappearance of murmurs to duration of illness follows a similar pattern in the small-dose and in the large-dose groups.

In regard to the apparent relation of frequency of disappearance of murmurs to duration of illness, consideration must be given to the possibility that, through natural selection, variation in severity of disease entered into the picture and influenced results. As previously pointed out,[2] patients with mild rheumatic fever may not have continued to have active disease long enough to be included in the groups of long duration, which, in contrast to those of short duration, may therefore have been weighted with more severe cases of rheumatic fever. On this basis alone, the cases of long duration might be expected to show a higher frequency of persistent murmurs.

On the other hand, all of the patients in this study presented signs of definite heart disease at the time therapy was started; therefore they cannot be considered to be cases of mild rheumatic fever. Furthermore, the difference in frequencies of disappearance of murmurs among those ill for a relatively short period and among those ill for a long period is so striking that it is difficult to accept natural selection as the only explanation. Finally, natural selection alone would not account for the differences in the frequency of disappearance of murmurs for those patients treated with large doses of hormones and those treated with small doses.

From the foregoing discussion, it is evident that final conclusions are not yet justified. Nevertheless, the data presented here suggest that results of hormone therapy in rheumatic fever are related to the time allowed to elapse before treatment is started, to the dosage of the hormone, and to the duration of therapy. The data also emphasize the importance of taking into consideration duration of illness, dosage of drugs used, and duration of treatment in any study aimed at comparing therapeutic agents in rheumatic fever.

Summary

Of 160 rheumatic fever patients under the age of 17 years who were treated with variable doses of ACTH or cortisone for varying lengths of time, 88 patients were in their initial attack of rheumatic fever and had definite signs of carditis.

The frequency of complete disappearance of

significant murmurs in 41 patients treated with relatively small doses of hormones was compared with that in 47 patients treated with relatively large doses of hormones. Results were related to the duration of illness prior to beginning of therapy.

In both the small-dose and the large-dose groups, the shorter the duration of illness prior to start of therapy the greater the frequency of disappearance of all significant murmurs. It was also noted that the frequency of disappearance of significant murmurs in the large-dose group was consistently greater than that in the small-dose group.

Data presented here suggest that results of hormone therapy in rheumatic carditis are related to the time allowed to elapse before treatment is started, to the dosage of the hormones, and to the duration of therapy.

Summario in Interlingua

In un serie de 160 patientes de febre rheumatic—omnes de etates de infra 17 annos e omnes tractate con ACTH o cortisona in varie doses e durante varie periodos—88 habeva lor attacco initial de febre rehumatic e monstrava definite signos de carditis.

Le frequentia del disparition complete de significative murmures in patientes tractate con relativemente basse doses del hormones (41 casos) esseva studiate in comparation con le frequentia del disparition complete de tal murmures in patientes tractate con relativemente alte doses del hormones (47 casos). Le resultatos esseva relationate al duration del morbo ante le institution del therapia.

In ambe gruppos—illo a basse e illo a alte doses—il esseva constatate que quanto plus breve esseva le duration del morbo ante le institution del therapia, tanto plus alte esseva le frequentia del disparition de omne murmures significative. Esseva etiam notate que le frequentia del disparition de murmures significative esseva regularmente plus alte in le gruppo a grande doses que in le gruppo a parve doses.

Le datos hic presentate pare indicar que le resultatos del hormonotherapia in carditis rheumatic depende (1) del tempore passate ante le initiation del tractamento, (2) del dosage de hormones administrate, e (3) del duration del curso therapeutic.

REFERENCES

1. Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F., and Kendall, E. C.: Effects of adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on the acute phase of rheumatic fever: preliminary report. Proc. Staff Meeting, Mayo Clinic **24:** 277, 1949.
2. Massell, B. F.: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis. New England J. Med. **251:** 183, 221, and 263, 1954.
3. The treatment of acute rheumatic fever in children. A cooperative clinical trial of ACTH, cortisone and aspirin. Circulation **11:** 343, 1955, and Brit. M. J. **1:** 555, 1955.

Withering's introduction of the use of the foxglove for treating patients with congestive heart failure must be regarded as one of the great milestones of scientific medicine. Decoctions and infusions of the leaves and of the roots of various flowering plants had been in vogue since prehistoric times, and folk remedies were as numerous as the communities into which human beings had divided themselves. Mandrake leaves were used in ancient China to relieve pain. Tea came into vogue as a stimulating beverage at the beginning of the seventeenth century. As a specific remedial agent there is only one other with which digitalis can be compared—the alkaloid derived from cinchona bark which had a checkered career for three hundred years before digitalis was discovered, but unfortunately cinchona during that long interval had no dispassionate Withering to espouse its cause.—John F. Fulton. *The Place of William Withering in Scientific Medicine.* J. Hist. Med. & Allied Sc., **8:** 10, 1953.

The Use of the Lead-Field Concept in the Development of Leads Satisfactory for Vectorcardiography. I. The Sagittal Lead

By ERNEST W. REYNOLDS, JR., M.D., JEROME F. CORDES, M.D., PARK W. WILLIS, III, M.D., AND FRANKLIN D. JOHNSTON, M.D.

After a brief discussion of the lead field concept and an illustration of its application using a Teledeltos paper model, studies carried out on patients, employing multiple electrode or grid arrangements located over the precordium and the left posterior chest, to obtain the sagittal component of cardiac electromotive forces (e.m.f.'s), are described. On the basis of these observations, a minimum of 15 properly arranged and connected electrodes should be employed in the anterior electrode system but fewer will be needed posteriorly. A scheme, using 63 electrodes mounted in sponge rubber, has been devised to simplify the grid arrangement.

SOME of the enthusiasm of a few years ago about the value of spatial vectorcardiograms in clinical diagnosis has died down recently and is being replaced by studies being carried out by competent groups or individuals, including both biophysicists and physicians, in an attempt to answer some of the basic questions that must be satisfactorily settled before vectorcardiography can be considered to be much of a science.

Everyone would agree that vectorcardiograms should be taken with leads or lead systems that give good representations of the cardiac electromotive forces (e.m.f.'s) in transverse, vertical, and sagittal directions, but there is no general agreement regarding which, if any, of the several methods proposed for the purpose are satisfactory. The sentiment seems to be increasing that neither the original scheme proposed by Duchosal and Sulzer[1] and modified by Grishman and associates[2] nor the tetrahedron employed by Burch and associates[3] and others give accurate vectorcardiograms. If several experts in the field of vectorcardiography were asked why the systems mentioned are not satisfactory, different answers involving matters like eccentricity of the mean cardiac dipole and unsuitable lead coefficients would be given, and all these replies would be correct and quite logical from the point of view of each of these individuals. Our answer to this query would be a very simple one; namely, that the lead fields associated with most of the leads in question are obviously unsuitable and cannot give good transverse, vertical, or sagittal components of the mean cardiac voltages.

The lead vector proposed by Burger and vanMilaan[4] several years ago is the basis of many important recent studies on electrocardiographic leads. Because it involves the concept of a single equivalent dipole in the heart, it has naturally led to extensive studies, partly in human beings and partly in models, to prove that portions, at least, of the electrocardiogram can be accurately represented by a single dipole, and further to establish the location of this dipole within the heart. Although much of this work is important and worthwhile, it seems to us that many of the investigators are pursuing their studies without

From the department of Internal Medicine, University of Michigan Medical School, Heart Station, University Hospital, Ann Arbor, Mich.

Some material in these papers was presented in abbreviated form at the meetings of the Central Society for Clinical Research in Chicago in October 1953 and before the Second International Congress of Cardiology in Washington, D. C., in September 1954.

These studies have been made possible largely with the use of funds given to the late Dr. Frank N. Wilson by the S. S. Kresge Foundation, and also by a grant from the U. S. Public Health Service (Grant HT-5114).

full appreciation of the lead-field concept and its advantages in estimating the behavior of leads of any kind and in the design of better ones, especially for vectorcardiography.

This is not the place for a detailed discussion of the lead field and its value, but readers interested in this subject are referred to papers by McFee and Johnston.[5] It should be pointed out, however, that the lead field not only extends the lead-vector concept to the entire heart, *thereby eliminating the need to assume the existence of a single dipole, equivalent to all cardiac e.m.f.'s*, but provides a method which is simple and easy to use.

In this paper and the ones that follow, leads or lead systems are described that the authors believe to be ideal for vectorcardiography. This first article is devoted to a discussion of a system for the anteroposterior or sagittal component of the cardiac e.m.f.'s. This component is considered first because the arrangement to obtain it illustrates the use of the lead field particularly well and also because most of the leads commonly employed to obtain it are not very good ones. Before the methods used on patients are described, an illustration of the principle employed, using Teledeltos paper,* is presented.

Figure 1 is a model of the sagittal view of the human torso made nonhomogeneous after the method of Brody and Romans.[6] Essentially, it consists of three layers of Teledeltos paper insulated from one another with photographic mounting paper except for a one centimeter margin on the underside of the two top layers. These margins are electrically bonded with a mixture of silver print ink, amyl acetate, and polyester coil dope, so that each layer conducts approximately one third of the current. The second layer contains cutouts for the lungs, and the third layer consists only of the heart and great vessels. By this process the lungs have one third the conductivity of heart and great vessels, and the chest wall has a conductivity halfway between that of lungs and heart. The electrode system to obtain the sagittal component from this model is provided by 10 uniformly spaced electrodes on the anterior and posterior surfaces of the chest, each attached by a 50,000 Ω resistance to a common terminal. The resistance from any one electrode to the electrode on the opposite side of the manikin is of the order of 4,500 ± 1000 Ω. Therefore, the 50,000 Ω resistance in each arm of the electrode system is sufficiently large to insure a reasonably uniform current field. To determine this field in the model, a 125-volt battery was attached to electrodes V_A and V_P and isopotential lines were carefully plotted with the two probes of a vacuum-tube voltmeter. After the isopotential lines were

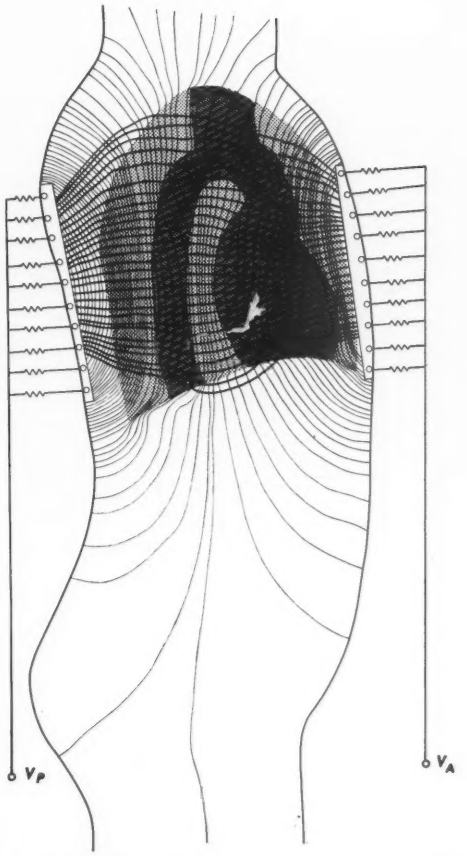


FIG. 1. The lead field of the proposed sagittal lead in a two-dimensional nonhomogeneous model. Except for a concentration of the lead-field lines near the apex, the field is nearly uniform and horizontal through all regions of the heart.

* This special paper with a uniformly conducting surface has been available through the courtesy of the Western Union Company.

mapped, the current lines were drawn perpendicular to them, and these, of course, constitute the lead field.

Inspection of figure 1 indicates that the general course of the lead field through the heart is anteroposterior in direction and, except for the apical region where some curvature is present, the electrode system in question would have excellent sensitivity for desired sagittal components and little for vertical components of cardiac voltages. The concentration of lead-field lines near the apex suggests that this electrode system would record an e.m.f. located in this region with somewhat greater amplitude than an equal and similarly oriented e.m.f. located higher in the heart. It must be remembered, however, that curvature and lack of uniformity in the lead field in the model are due entirely to assumed differences in conductivity between areas that represent the heart and great vessels, the lungs, and subcutaneous tissues, and it is likely that such large differences do not exist in living human subjects. Furthermore, studies bearing on this point done with fluid mappers by McFee, Stow, and Johnston[7] suggest that variations in tissue conductivity have only minor effects on the character of the lead field within the heart.

If a model like figure 1 is made, using a horizontal section through the middle of the heart, instead of the sagittal view, and if the lead field is obtained with nine equally spaced and similarly connected electrodes over the anterior and posterior cardiac areas, the field will again be essentially anteroposterior in direction and reasonably uniform.

It is clear that the ideal lead for the sagittal component in human subjects should be some sort of multiple electrode or grid system, and only details remain to be decided. Some of the questions to be settled are: How many electrodes will be required, and how should they be arranged on the precordium and on the left posterior chest? What should be the size of the resistances connected to the individual chest electrodes and to the common anterior and posterior lead terminals? Finally, can some scheme be devised for application of the multiple electrode arrangement that will be simple and quick? The balance of this paper is largely concerned with these matters.

A few words should be said about the use of large, thin, flexible metal plates rather than multiple small electrodes (connected to single terminals through large resistances) for the anterior and posterior electrodes. At first sight this type of arrangement might seem ideal, and something of this kind may be shown to be useful. The big problem is, of course, to be sure whether such electrodes have a uniform contact resistance over their entire surface. Even with careful preparation of the skin over which the electrode is placed, there is no certainty that even approximately uniform resistance is obtained, and there is no direct way to test

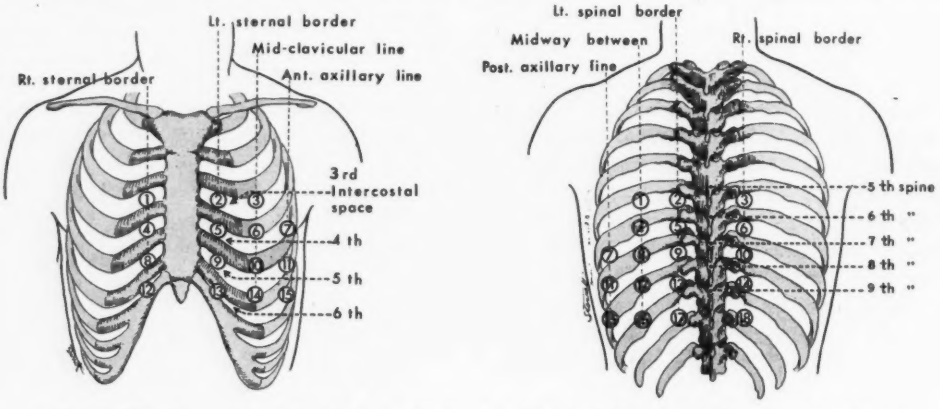


FIG. 2. The placement of electrodes on the front and back of the chest in the 15 point grid system is accomplished so that the grid overlaps the projection of the heart on the chest wall.

this. We have tried such electrodes on a few occasions, and the records obtained have been similar but not identical with those secured with multiple electrode grids. We suspect that simple metal plates would give a better antero-posterior component than schemes now in current use, but their value remains to be determined by further comparisons with results obtained with multiple electrode systems.

Method

Electrocardiographic studies using two different schemes for application of multiple electrodes for obtaining the sagittal component of cardiac voltages were done on 39 individuals, some with normal and some abnormal hearts. In the first group 15 small (flat buttons of solder about 5 mm. in diameter) electrodes were placed over the precordial area and on the left posterior chest wall as shown in figure 2. Each of these electrodes was carefully applied with electrode paste, fastened securely in position with Scotch tape, and connected through large resistances to single anterior and posterior terminals. Since the resistance measured between corresponding single anterior and posterior electrodes was found to be approxmately 22,000 Ω, but varied considerably, 50,000 Ω resistances originally employed were replaced by resistances of 1,000,000 Ω, to be sure that variations in skin resistance at individual electrodes would not disturb the lead field of the electrode system. After an electrocardiogram had been recorded with all of the electrodes in the circuit, additional tracings were taken following progressive reduction in the number of electrodes in use. This procedure was carried out for both the anterior and posterior grids, and as the electrodes were reduced in number, they were kept as well distributed as possible over the area covered by the original 15.

Because application of 30 individual electrodes is time consuming and would not be a practical method for routine vectorcardiographic work, a simpler and probably better method for obtaining the sagittal component was devised. In the second group of patients studied, the arrangement illustrated in figure 3 was employed. The anterior and posterior electrode systems were alike; each consisted of a rectangular piece of sponge rubber measuring 10 by 12 inches, in which nine rows of brass machine screws were mounted with the heads (the contact electrodes) 1 inch apart. Seven screws were used in each row, so that a total of 63 electrodes were available for both anterior and posterior grid arrangements. Each electrode was connected through a resistance of 1,000,000 Ω to a common terminal. A second piece of sponge rubber of the same size was fastened to the first to protect the wires soldered to the shanks of the machine screws and provide a certain amount of "give" when the electrodes were placed on the chest. Before the electrodes were applied, the skin was prepared by rubbing with alcohol, followed by ether. After electrode paste was applied to the head of each machine screw, the entire unit was placed on the left anterior and posterior chest with the electrodes centered as well as possible over the cardiac areas. Good contact with the posterior electrodes was assured by having the patient lie on them. Several strips of wide gauze wrapped around the subject and electrode assemblies and sand bags over the anterior unit provided good approximation between the anterior electrodes and the precordium. Impressions of each electrode in the skin after removal of the assemblies were evidence of good contact. Although we anticipated some difficulty with this electrode arrangement, none occurred in any of the 18 subjects on whom it was used. The resistance measured between two corresponding individual electrodes was quite variable but averaged around 50,000 Ω, and the resistance of the full grid (including the 1 meg.ohm resistances) was around 100,000 Ω.

In the second group of subjects, like the first, electrocardiograms were taken with all electrodes in the circuit, and then tracings were taken as the number of active electrodes was decreased in both anterior and posterior grids.

All electrocardiograms were taken with a Sanborn Twin-Beam Electrocardiograph, and a simultaneous limb lead, usually lead II, was recorded with each sagittal lead. The effect of reducing the number of active electrodes from the full grids could have been studied in each group of patients by recording vectorcardiograms in the horizontal and sagittal planes, and a few such records were taken. It was thought, however, that the simplest way to find out how many electrodes must be used in both anterior and posterior grids was to study the changes in conventional electrocardiograms representing the sagit-

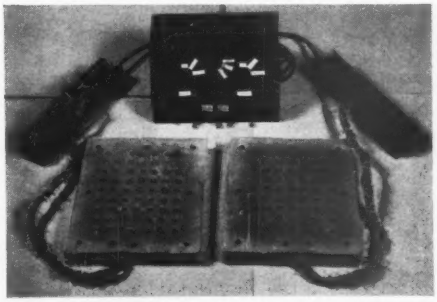


Fig. 3. Sixty-three electrodes mounted in rectangular pieces of foam rubber comprise the anterior and posterior grid electrodes for the second group of patients. The switch arrangement permits uniform reduction in the number of electrodes used in the circuit.

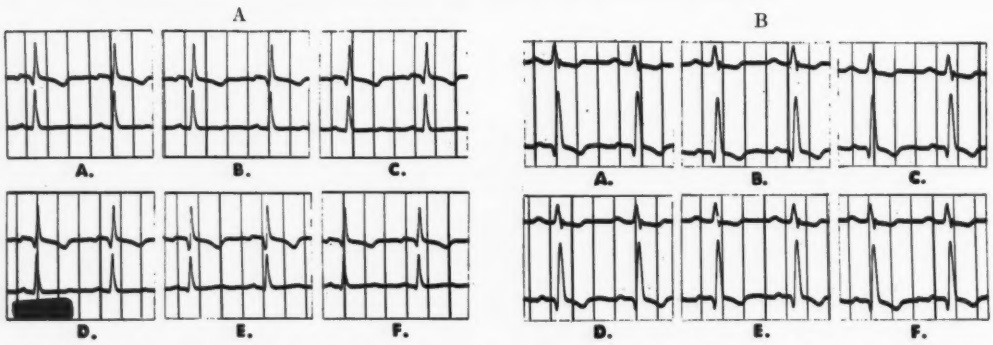


FIG. 4. *A*. An example of the tracings taken using the 15 point sagittal lead illustrated in figure 2. Reduction of the number of electrodes in successive tracings as shown in table 1 caused erratic changes in phase, voltage and appearance of the Q and R waves. Lead I, recorded simultaneously, is the *lower* tracing in this figure. *B*. An example of the tracings taken with the 63 point grid electrode. Reduction in the number of electrodes (table 2) results in only minor changes. Lead II, recorded simultaneously, is the *upper* tracing in this figure.

TABLE 1.—*Fifteen Point Grid Electrode System*

Experiment Description of Lead (Fig. 2)	Fig. 4A	PR	QRS	Peak Q	Peak R	Height of Q	Height of R
		sec.	*sec.*	*sec.*	*sec.*	*mm.*	*mm.*
ES-10 Full grid (not including electrodes 1, 2, 3 posteriorly)	A	.1502	.0916	.0328	.0638	3.75	15.75
V_P (Solid plate)—V_A (Solid plate)		.1567	.0883	.0298	.0583	4.00	18.50
Posterior electrodes being removed							
electrodes 7, 11, 15 removed	B	.1595	.0867	.0235	.0473	3.75	16.50
electrodes 6, 10, 14, 18 removed	C	.1510	.0844	.0264	.0542	2.90	16.00
electrodes 5, 9, 13, 17 remain	D	.1468	.0827	.0290	.0571	3.90	16.20
electrode 9 remains		.1590	.0846	.0318	.0631	3.75	16.10
Anterior electrodes being removed							
electrodes 1, 4, 8 removed	E	.1720	.0716	.0340	.0654	5.00	16.00
electrodes 3, 6, 10, 14 removed	F	.1751	.0691	.0219	.0494	2.60	16.00
electrodes 7, 9, 11, 15 remain		.1560	.0874	.0318	.0655	3.00	18.80
electrode 9 remains		.1640	.0746	.0394	.0542	10.00	12.40

Diagnosis: Diabetes with Kimmelstiel-Wilson disease; aortic stenosis with left ventricular hypertrophy. Postmortem, left ventricle 17 mm., weight 460 Gm.

TABLE 2.—*Sixty-Three Point Grid Electrode System*

Experiment Description of Lead (Fig. 3)	Fig. 4B	PR	QRS	Peak Q	Peak R	Height of Q	Height of R
		sec.	*sec.*	*sec.*	*sec.*	*mm.*	*mm.*
FF-37 Full grid 63–63 electrodes	A	.168	.112	.0208	.0602	4.72	27.50
Posterior electrodes being removed							
63–35 electrodes	B	.170	.108	.0218	.0626	4.23	26.62
63–16 electrodes	C	.175	.110	.0192	.0610	4.27	26.54
Anterior electrodes being removed							
35–63 electrodes	D	.165	.108	.0202	.0610	4.95	27.30
16–63 electrodes	E	.168	.110	.0243	.0653	4.75	27.27
Anterior and posterior grid reduced							
35–35 electrodes		.168	.110	.0210	.0598	4.70	27.50
16–16 electrodes	F	.168	.110	.0208	.0626	4.82	26.61

Diagnosis: Hypertension with left ventricular hypertrophy.

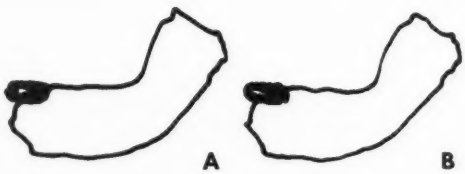


FIG. 5. Sagittal vectorcardiograms using the grid type electrodes. *A*. All 63 points are used. *B*. The number of active electrodes is reduced anteriorly and posteriorly to 16.

tal component as the number of active electrodes was progressively decreased.

A number of measurements of the tracings were made, including estimation of the P-R and QRS intervals, the size of the waves in the QRS complexes, and the time intervals between peaks of Q, R, and S in the sagittal lead and the beginning of the QRS complex in the simultaneously recorded limb lead. Amplitude measurements were, of course, corrected for errors in standardization, and most of the time intervals were measured with a Lucas comparator. Figure 4 shows records taken from a patient in each group illustrating the effect of decreasing the number of electrodes in the anterior grids. In figure 4A changes in form and amplitude are obvious on inspection, as the number of electrodes was decreased from the full grid of 15. On the other hand, in figure 4B there is little change in the sagittal electrocardiogram when the full grid of 63 electrodes was reduced to 16, the smallest number employed in this group.

Tables 1 and 2 illustrate the type of measurements made in the two groups, where the full grids consisted of 15 and 63 electrodes, respectively. These data support the tentative conclusions suggested by the tracings shown in figure 4. It is unnecessary to discuss these tables in detail, but a few important matters should be pointed out. As might be expected, table 1 shows that the number of electrodes in the posterior system can be considerably reduced without greatly altering the electrocardiogram, while a comparable change in the anterior grid caused definite alteration in the tracing. This situation is, of course, due to the fact that the heart lies much closer to the anterior than to the posterior chest wall, and it would be anticipated that fewer electrodes posteriorly would still give a lead field essentially uniform and of the proper direction through the heart.

RESULTS

Although it may be possible to use as few as nine or even six anterior electrodes and still obtain a fairly accurate sagittal electrocardiogram, it must be remembered that *the importance of the location of individual electrodes increases greatly as the number decreases*, and the proper location of a small number would vary greatly in different subjects. For this reason alone, we feel that a reasonably large number of electrodes is advisable in the anterior grid.

The results of the studies presented in table 2 supplement those of table 1. They indicate rather clearly that as many as 63 electrodes in the anterior grid are unnecessary and suggest that the minimal number tested, that is 16, may be satisfactory. From the theoretic standpoint, however, the large number should have some advantages, and with the sponge rubber assembly technic, it is not much more difficult to use them.

SUMMARY AND CONCLUSIONS

In a brief discussion of matters relating to electrocardiographic leads, particularly ones suitable for vectorcardiography, advantages inherent in the use of lead-field concept are pointed out. In this connection, it is emphasized that the lead field removes an important limitation imposed by use of the lead vector; namely, that cardiac e.m.f.'s must be assumed to be concentrated in a single equivalent dipole. The lead field within the heart actually gives the direction of lead vectors for e.m.f.'s located anywhere in this organ.

A study made with a model of the human torso in the sagittal plane using Teledeltos paper indicates that several uniformly spaced electrodes over the precordium and left posterior chest, each connected through large resistances to two terminals, create a lead system with a lead field of the type necessary for a good sagittal lead.

Results are presented of studies on human subjects using multiple electrodes in a grid arrangement over the precordium and left chest behind the heart as a method for securing the sagittal component of cardiac e.m.f.'s. These studies suggest that approximately 15 electrodes will be required in the anterior group if an accurate lead is to be obtained. The posterior grid may consist of fewer electrodes without seriously affecting the performance of the lead.

Since the application of 15 individual

electrodes is time-consuming and would not be practical for routine vectorcardiography, we have devised a special electrode arrangement consisting of large sheets of sponge rubber in which 63 brass machine screws, which serve as electrodes, are mounted. These electrode assemblies have proved to be quick and easy to use.

Summario in Interlingua

Es presentate un breve discussion de derivationes electrocardiographic, specialmente del typo usabile in vectocardiographia, con le objectivo de signalar le avantages inherente in le uso del concepto del campo de derivation. In iste connexion le facto es sublineate que le uso de ille concepto elimina un importante limitation in le application del vector de derivation, i.e. le limitation que on debe supponer que le cardiac fortias electromotive es concentrate in un sol dipolo equivalente. De facto, le campo de derivation intra le corde da le direction de vectores de derivation pro fortias electromotive de non importa qual location in ille organo.

Un studio executate per medio de un modello del torso human in le plano sagittal (usante papiro Teledeltos) indica que plure electrodos, uniformemente spatiate supra le precordio e le thorace sinistro-posterior e omnes connectite via alte resistentias con duo terminales, crea un systema de derivation con un campo de derivation del typo requirite pro un bon derivation sagittal.

Es presentate resultatos de studios in subjectos human, utilisante multiple electrodos de arrangiamento grilliforme supra le precordio e le thorace sinistre a retro del corde como methodo de assecurar le componente sagittal de cardiac fortias electromotive. Iste studios indica que circa 15 electrodos es requirite in le gruppo anterior si un derivation accurate debe esser obtenite. Le grillia posterior pote consister de minus electrodos sin que le efficacia del derivation es seriemente obstruite.

Considerante que le application de 15 electrodos individual consume multe tempore e es consequentemente impractic in vectocardiographia routinari, nos ha elaborate un special arrangiamento de electrodos consistente de grande placas de cauchu spongia in que es montate 63 vites de laton serviente como electrodos. Iste combinationes de electrodos se ha provate capace de manipulation rapide e facile.

REFERENCES

1. Duchosal, P. W., and Sulzer, R.: La Vectorcardiographie. Basle, S. Karger, 1949.
2. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial vectorcardiography: Technique for the simultaneous recording of the frontal, sagittal and horizontal projection. I. Am. Heart J. **41:** 483, 1951.
3. Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Spatial Vectorcardiography. Philadelphia, Lea & Febiger, 1953.
4. Burger, H. C., and van Milaan, J. B.: Heart vector and leads, I. Brit. Heart J. **8:** 157, 1946; II. **9:** 154, 1947; III. **10:** 229, 1948.
5. McFee, R., and Johnston, F. D.: Electrocardiographic leads. I. Introduction. Circulation **8:** 554, 1953; II. Analysis. **9:** 255, 1954; III. Synthesis. **9:** 868, 1954.
6. Brody, D. A., and Romans, W. E.: A model which demonstrates the quantitative relationship between the electromotive forces of the heart and the extremity leads. Am. Heart J. **45:** 263, 1953.
7. McFee, R., Stow, R., and Johnston, F. D.: Graphic representation of electrocardiographic leads by means of fluid mappers. Circulation **6:** 21, 1952.

Hereditary Obesity: Relation to Serum Lipoproteins and Protein Concentrations in Swine

By Lena A. Lewis, Ph.D., and Irvine H. Page, M.D.

The importance of heredity in determining the cholesterol, lipoprotein, and plasma protein levels has received insufficient attention. All of these have a greater concentration in the blood of short-fat (mesomorphic), castrate, male, miniature pigs than in long-lean (ectomorphic) animals. These differences seem to persist even when weight changes and growth are rapid. We believe that some of the wide variability of blood lipid levels in human beings is due to genetic factors in the heterogeneous human population on varied diets.

IN THE hereditary obese-hyperglycemic syndrome of mice, hypercholesterolemia occurs.[1] However, association of hypercholesterolemia with hereditary obesity in other species is not well documented. The present studies were made on miniature swine of the long-lean and short-fat strains to determine any association between body build and cholesterol-lipoprotein levels.

Methods and Material

Six dwarf swine, bred at the University of Minnesota and classified as long-lean or short-fat strains, were obtained when 12 weeks of age.* They were castrate males and had been immunized against cholera. They were fed a diet of ground oats, corn, and SMA formula† with multivitamins and extra vitamin D. Blood samples were taken every 2 weeks. Serum lipoproteins were determined ultracentrifugally at a density of 1.21, with KBr-NaCl as described by Lewis, Green, and Page.[2] Serum proteins were determined by the moving-boundary-electrophoresis method of Tiselius as modified by Longsworth,[3] with phosphate buffer at pH 7.8 and ionic strength of 0.16 μ. Cholesterol was measured by the method of Abell and associates,[4] free cholesterol by the Sperry and Webb[5] method, and phospholipids by the Youngburg and Youngburg technic.[6] Total protein was determined by the biuret method as modified by Sols.[7]

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

* Obtained from Dr. David C. England, Hormel Foundation, to whom we are indebted.

† Contains cow's milk protein, 1.5 per cent; lactose, 7 per cent; fat, 3.5 per cent; minerals and vitamins; and 20 calories per ounce. It is produced by Wyeth Laboratories, Philadelphia, Pa.

Results

The electrophoretic serum protein patterns of pigs showed clearly resolved albumin, α_2-, β- and γ-globulin fractions (fig. 1). The total protein concentration of the fat pigs was higher than that of the lean animals, due largely to a higher albumin and β-globulin concentration. These differences persisted throughout the 9-month study, which covered a period of rapid growth for the pigs. The average total protein of the lean pigs at 14 weeks of age was 4.50, and at 34 weeks was 5.88 Gm./100 ml., while for the fat pigs it was 4.81 and 6.73 Gm./100 ml.

Both strains of pigs showed an increasing concentration of γ-globulin with growth, that of the lean pigs from 0.69 at 14 weeks to 0.91 at 34 weeks of age, and of the fat pigs from 0.42 to 1.04 Gm./100 ml. The concentration of α_2-globulin for both strains was similar and showed no consistent change during the study.

The total serum cholesterol of the fat pigs was higher than that of the lean, with an average of 149 and 106 mg./100 ml. of serum, respectively, at 14 weeks; and 176 and 126 mg., respectively, at 34 weeks. The concentration of phospholipid phosphorus of the fat pigs was also higher, averaging 7.3 mg./100 ml. at 14 weeks and 8.6 mg. at 34 weeks; while that of the lean pigs was 4.9 and 6.4 mg./100 ml., respectively.

The early studies were made on serum obtained approximately 5 hours after feeding to permit frequent feeding of the young animals.

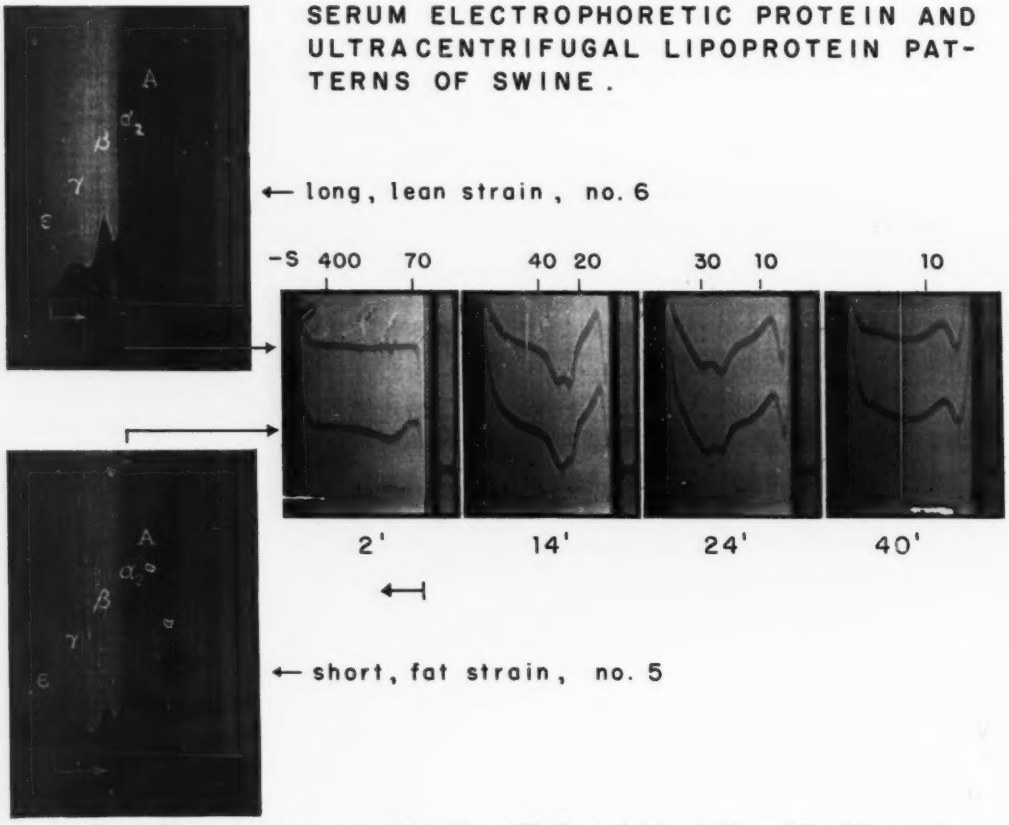


FIG. 1. Electrophoretic serum protein patterns (Tiselius technic) and ultracentrifugal lipoprotein patterns of swine of long-lean and short-fat strains.

Later, samples were collected 18 hours after food ingestion.

The lipoprotein pattern of the pig (fig. 1) showed varying amounts of poorly resolved, very low density $-S > 400$ material (i.e., chylomicrons), low density $-S$ 70–400 and 40–70 components, clearly defined fractions with flotation rates between 25–40 and 15–25, and high density fraction $-S$ 1–10. The concentration of $-S$ 15–25 is greater than in most other species that have a component with a similar flotation rate. The difference between the fasting and nonfasting lipoprotein patterns was a reduction of the very low density $-S > 400$ component in the fasting samples.

The low density lipoproteins are present in greater concentration in the fat than in the lean animals, as are the $-S$ 15–40 fractions. The high density, $-S$ 1–10, fraction was of similar concentration in both strains. A protocol on fat pig No. 5 and lean No. 6 (tables 1 and 2) shows the persistent differences between the 2 strains throughout the 9 months of study.

The concentration of the $-S$ 15–40 components of both strains increased during the period of study. The average concentration of $-S$ 15–40 of the lean pigs at 14 weeks of age was 105 mg. and at 34 weeks was 206 mg./100 ml., while that of the fat animals was 129 mg. and 286 mg., respectively. Changes in concentration of the other components could not be correlated with age.

The long-lean pigs gained an average of 0.9 Kg. weekly in body weight during the first 20 weeks, while the short-fat animals averaged 1.7 Kg. (fig. 2). Since aureomycin in low con-

centration has been shown to increase the rate of weight gain of swine,[8] this antibiotic was added to the diet in the amount of 100 mg./10 lbs. of dry feed. With this supplement, the weight gain of the lean pigs for the next 10 weeks was accelerated to 2.1 Kg./week, and of the fat to 2.0 Kg. Despite the accelerated weight gain, the lean pigs retained their characteristic long-lean look as compared to the fat ones (fig. 3). The differences in serum protein, cholesterol, and lipoproteins also persisted.

TABLE 1.—*Electrophoretic Serum Protein Fractions with Phosphate Buffer pH 7.8, Ionic Strength 0.16 by Moving Boundary Method, of Fat and Lean Miniature Pigs*

Date	Gm./100 ml.					Hours after ingestion of food
	Total protein	Albumin	α_2-Globulin	β-Globulin	γ-Globulin	
Pig #5; Short-Fat Strain						
8/11/54	5.03	2.83	1.03	0.80	0.37	5
9/23/54	5.49	3.15	0.95	0.83	0.56	5
10/21/54	6.11	3.35	1.09	0.87	0.80	5
1/5/55	6.68	4.00	1.21	0.69	0.78	5
3/3/55	7.05	3.72	1.18	1.08	1.07	18
3/31/55	6.96	4.01	0.74	1.18	1.03	18
Pig #6; Long-Lean Strain						
8/11/54	4.73	2.21	1.10	0.61	0.81	5
9/23/54	5.59	2.49	1.45	0.98	0.67	5
10/21/54	5.31	2.38	1.41	0.94	0.58	5
1/5/55	5.55	3.12	0.96	0.98	0.49	5
3/3/55	6.44	3.24	1.19	1.17	0.84	18
3/31/55	6.68	3.49	1.14	1.12	0.93	18

DISCUSSION

The changes in the serum protein pattern of the pigs during growth, i.e., increased albumin and γ-globulin concentration, are similar to those occurring in young dogs from the time of weaning until full growth.[9]

The differences observed in serum protein and lipoprotein pattern of the 2 strains of pigs are found at a young age and persist. This indicates the permanence and importance of hereditary factors in establishing the protein-lipoprotein spectrum.

The finding of differences in lipoprotein and cholesterol concentration in 2 strains of pigs of similar age and on identical diets may help to explain the great range of normal values found in the heterogeneous human population on varied diets. The results indicate the inadmissibility of using different strains of animals for protein or lipoprotein studies without careful determination of their normal levels.

TABLE 2.—*Serum Lipoprotein, Cholesterol, and Phospholipid Concentrations of Miniature Swine (Short-Fat #5 and Long-Lean #6) During Growth*

Date	*mg./100 ml. of serum*										Hours after ingestion of food
	Total cholesterol	Free cholesterol	Phospholipid	Cholesterol: phospholipid ratio	Serum Lipoproteins						
						−S >400	−S 70–400	−S 40–70	−S 25–40	−S 15–25	−S 1–10
Pig #5; Short-fat Strain											
8/11/54	125	25	5.8	0.86	+++	38	0	71	45	158	5
9/23/54	234	41	12.8	0.73	+++	56	0	106	106	282	5
10/21/54	227	49	12.4	0.73	+++	124	0	106	82	270	5
1/ 5/55	247	57	10.8	0.91	+++	162	19	161	141	220	5
3/ 3/55	163	45	8.9	0.73	+	183	0	162	114	242	18
3/31/55	159	33	6.8	0.94	+	120	42	146	114	212	18
Pig #6; Long-Lean Strain											
8/11/54	111	19	6.7	0.66	++	7	0	56	33	212	5
9/23/54	125	16	8.0	0.63	++	28	7	35	47	169	5
10/21/54	136	30	10.6	0.52	++	45	0	47	52	199	5
1/ 5/55	94	14	7.4	0.51	++	0	0	47	50	190	5
3/ 3/55	105	19	5.2	0.81	0	0	0	80	109	225	18
3/31/55	118	19	6.4	0.74	0	21	21	50	71	246	18

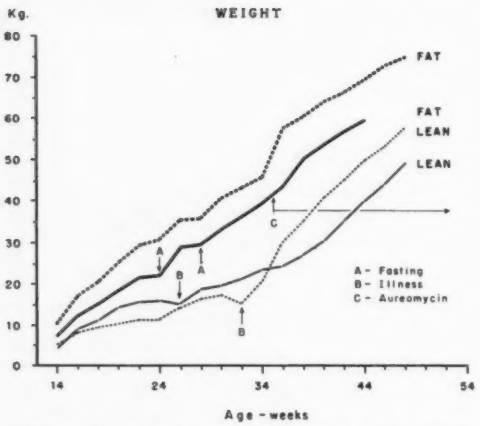


FIG. 2. Comparative weight gain of long-lean and short-fat swine.

FIG. 3. Dwarf swine of short-fat (mesomorph type) and long-lean (ectomorph type) at 26 weeks of age, upper pictures, and 44 weeks, lower picture.

Little evidence has been presented in the past to indicate the importance of hereditary factors in determining normal serum protein or lipoprotein variations within a species. Slightly better documentation has been advanced for cholesterol variations (Adlersberg, Parets, and Boas[10]). The recent finding of significantly higher γ-globulin and lower albumin and β-globulin concentrations in Navajo (Page, Lewis, and Gilbert[11]) and Peruvian Indians than in the Caucasian American population suggests the possibility of a hereditary factor. Young, Wolfson, and Cohn[12] found agammaglobulinemia in a series of patients and suggested that the syndrome may be due to congenital or to acquired factors, as one of the patients had no lymphocyte abnormalities and relatives of both sexes manifested hypergammaglobulinemia. The finding of agammaglobulinemia in siblings by Brem and Morton[13] also lends support to the hypothesis that γ-globulin formation may be genetically influenced.

The long-lean pigs could be considered an ectomorph type, while the short-fat animals have many of the characteristics associated with the mesomorph. Our data on pigs are not unlike those on human beings, where the ectomorph has lower levels of cholesterol than the mesomorph (Gertler and White[14]).

Appreciable numbers of swine show arteriosclerotic lesions, approximately 13 per cent at 1 to 2 years of age and 25 per cent at 2 to 3 years.[15] Any relation between the incidence of lesions and the somatotype to which the swine belonged would be of great interest.

SUMMARY

Electrophoretic serum protein fractions, ultracentrifugally determined lipoproteins, and cholesterol, have been estimated on 6 castrate male, miniature swine, 3 of the long-lean (ectomorph) and 3 of the short-fat (mesomorph) strain. Higher concentrations of total serum protein, albumin, cholesterol, and lower density, $-S > 400$, 40–400, and 20–40, lipoproteins are present in fat pigs than in lean pigs. These differences persist throughout the period of rapid growth, when the relative rate of weight gain is similar and the diets are identical. The importance is emphasized of physical habitus or somatotype in the establishment of serum lipoprotein and protein patterns, in animals of like species but different genetic strain.

SUMMARIO IN INTERLINGUA

Esseva estimate le concentrationes seral de (1) le fractiones proteinic (in studios electrophoretic), (2) le lipoproteinas (post ultracentrifugation), e (3) le cholesterol in 6 castrate porcos mascule del racia "miniatura." Tres del animales representava un lineage longe e magre

(ectomorphe), e 3 esseva de un lineage curte e grasse (mesomorphe). Le porcos grasse—in comparation con le porcos magre—habeva plus alte total concentrationes seral de proteina, albumina, e cholesterol e plus basse densitates lipoproteinic ($-S > 400$, 40–400, e 20–40). Iste differentias persisteva durante le periodo de rapide crescentia con dietas identic e simile valores relative del augmento de peso. Es sublineate le importantia del typo physic (i.e. del somatypo) in determinationes del valores seral de lipoproteinas e proteinas in animales del mesme specie sed de varie lineas genetic.

ACKNOWLEDGMENT

We wish to thank Dr. Stanton M. Hardy, Lederle Laboratories Division, American Cyanamid Company, for the aureomycin used and Dr. George E. Farrar, Jr., Wyeth Laboratories, for the SMA formula fed the pigs.

The technical assistance of Mrs. Louise Crouder, Miss Joanna Jones, and Mr. Stephan Barany is gratefully acknowledged.

REFERENCES

1 MAYER, J., AND JONES, A. K.: Hypercholesteremia in the hereditary obese-hyperglycemic syndrome in mice. Am. J. Physiol. **175:** 339, 1953.

2 LEWIS, L. A., GREEN, A. A., AND PAGE, I. H.: Ultracentrifuge lipoprotein pattern of serum of normal, hypertensive, and hypothyroid animal. Am. J. Physiol. **171:** 391, 1952.

3 LONGSWORTH, L. G.: A modification of the Schlieren method for use in electrophoretic analysis. J. Am. Chem. Soc. **61:** 529, 1939.

4 ABELL, L. L., LEVY, B. B., BRODIE, B. B., AND KENDALL, F. E.: Simplified method for estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem. **195:** 357, 1952.

5 SPERRY, W. M., AND WEBB, M.: Revision of Schoenheimer-Sperry method for cholesterol determination. J. Biol. Chem. **187:** 97, 1950.

6 YOUNGBURG, G. E., AND YOUNGBURG, M. V.: Phosphorus metabolism; system of blood phosphorus analysis. J. Lab. & Clin. Med. **16:** 158, 1930.

7 SOLS, A.: An improved biuret reaction of proteins and the two-standard colorimetry. Nature **160:** 89, 1947.

8 WALLACE, H. D., ALBERT, L. T., NEY, W. A., COMBS, G. E., AND CUNHA, T. G.: Effects of reducing and discontinuing aureomycin supplementation during the growing-fattening period of pigs fed corn-peanut, corn-soybean meal, and corn-cottonseed meal rations. J. Animal Sc. **12:** 316, 1953.

9 LEWIS, L. A.: Changes that occur in six plasma proteins during growth of dog. J. Biol. Chem. **162:** 473, 1946.

10 ADLERSBERG, D. A., PARETS, A. D., AND BOAS, E. P.: Genetics of atherosclerosis; studies of families with xanthoma and unselected patients with coronary disease under the age of 50 years. J.A.M.A. **141:** 246, 1949.

11 PAGE, I. H., LEWIS, L. A., AND GILBERT, J.: Plasma lipids and proteins and their relationship to coronary disease among Navajo Indians. Circulation **12:** 675, 1956.

12 YOUNG, I. I., WOLFSON, W. I., AND COHN, C.: Studies in serum proteins, agammaglobulinemia in the adult. Am. J. Med. **19:** 222, 1955.

13 BREM, T. H., AND MORTON, M. E.: Defective serum gammaglobulin formation. Ann. Int. Med. **43:** 465, 1955.

14 GERTLER, M. M., AND WHITE, P. D.: Coronary Heart Disease in Young Adults. A Multidisciplinary Study. Cambridge, Harvard University Press, 1954.

15 GOTTLIEB, H., AND LALICH, J. J.: The occurrence of arteriosclerosis in the aorta of swine. Am. J. Path. **30:** 851, 1954.

The physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practising a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.—WILLIAM OSLER. *Teaching and Thinking.* Montreal M. J., 1895.

The Relation of Cardiovascular Phenomena to Metabolic Changes in a Patient with Chronic Hypokalemia

By Edward J. Huth, M.D., and Russell D. Squires, M.D.

Cardiovascular phenomena were studied and correlated with metabolic data in an adult male with chronic hypokalemia. The appearance and disappearance of postural hypotension, the changes in heart rate, the S-T segment shifts, and the U-wave amplitudes correlated well with the changing serum potassium level during experimental acute potassium depletion. QRS and T-wave changes could not be correlated with metabolic data. Comparison with the cardiovascular manifestations of experimental potassium depletion in normal subjects suggested that this patient had a chronic potassium depletion of at least 300 mEq.

CLINICAL interest in the effects of hypokalemia on the circulatory system has been focused mainly on changes in electrocardiographic patterns and on relationships to digitalis effects. For the most part, too, the interest has been aroused by observations on patients having acute hypokalemia. The present paper is concerned with cardiovascular phenomena observed during more than 4 years in a patient with chronic hypokalemia. These phenomena are examined in relation to the metabolic disturbances.

The clinical problem presented by the patient was recurrent muscle weakness that for over a decade had occurred in episodes lasting from 3 to 4 days, at first monthly, later as often as weekly. The relation of the muscle weakness to hypokalemia was established during the patient's first visit to this hospital, 10 years after the onset of his illness. During the next 4 years, the period covered by this study, the serum potassium concentration did not rise above 3.0 mEq./L., despite potassium chloride medication, though the latter freed the patient almost entirely from the attacks of paralysis.

From the Chemical Section of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Aided by Grant H-340 of the National Heart Institute of the United States Public Health Service and by the C. Mahlon Kline Fund for Development in the Department of Medicine.

Part of the work reported was done during Dr. Huth's tenure of a Life Insurance Medical Research Fund Post-Doctoral Fellowship, 1952-53, and Dr. Squires' tenure of a J. Allison Scott Fellowship, Department of Research Medicine, University of Pennsylvania, 1952-53.

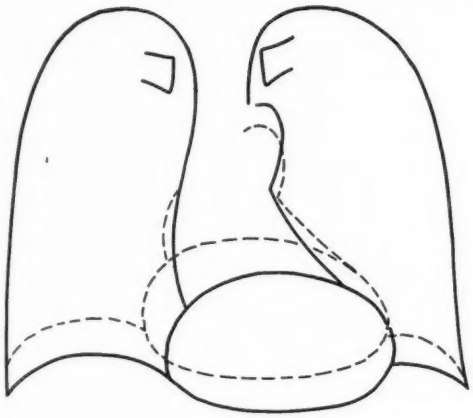
Case History

H. B., a man, was first seen by the authors when he was 38 years old. He had suffered since the age of 28 from recurrent muscle paralysis in the arms and legs. Each episode was heralded by dryness of the throat, lasted 3 to 4 days, and spontaneously remitted. The frequency of the episodes was monthly at first and later weekly. At the age of 14 or 15 the patient had passed "bloody" urine once, but at that time had felt otherwise well.

At the initial physical examination the recumbent blood pressure was 130/80. The head was tilted back and to the left in the characteristic position of torticollis. The right eye showed a superior oblique muscle palsy. The heart rate was 80/min. and the rhythm was normal. The heart size was normal. A soft grade 1 systolic murmur was heard in the pulmonic area where the second sound was louder than in the aortic area. The slightly enlarged liver was not tender.

The blood showed slight hemoconcentration and the bone marrow was hypercellular. The specific gravity of the urine was 1.004, with an alkaline reaction, 0 to +1 albumin and a few white and red cells and finely granular and hyaline casts in the sediment. The urea clearance was 38 per cent of normal and the phenolsulfonphthalein excretion was 36 per cent in 2 hours. Intravenous urography showed enlargement of both renal shadows, poorly outlined calyceal systems, and delayed dye excretion.

Blood chemical studies showed a serum potassium of 2.8 mEq./L., sodium of 136 mEq./L., CO_2 content of 30–33.4 mM/L., chloride of 89 and 91 mEq./L., blood urea nitrogen of 17 – 26 mg./100 ml., and serum creatinine of 1.9 mg./100 ml.



	TDC cm.	TDH cm.	FAH cm.²
---- 4-4-52	24	13	74
—— 4-5-52	24	12	69

FIG. 1. Orthodiagrams showing elevation of the diaphragm at the end of an acute potassium depletion and normal position early in recovery. *TDC* = transverse diameter of the chest, *TDH* = transverse diameter of the heart, *FAH* = frontal area of the heart.

Cutaneous ("arterialized") blood showed a cell volume of 51 per cent, pH of 7.48, CO_2 content of 19.6 mM/L., CO_2 pressure of 34 mm. Hg, and buffer base of 51.5 mEq./L.

Treatment with potassium chloride rapidly relieved the muscular weakness and increased muscle action potentials in the affected groups. After discharge from the hospital, the patient continued to take potassium chloride, about 4 to 7 Gm. a day. The frequency of episodes of muscle weakness was sharply reduced to 1 or 2 a year. Nevertheless, hypokalemia persisted at levels of 2.0 to 2.8 mEq/L. Larger doses of potassium chloride induced diarrhea.

RESULTS

During later admissions to the hospital, the muscle weakness was experimentally reproduced by acute reduction of potassium in the patient's intake, while metabolic balance studies were carried out. The authors concluded that the patient's hypokalemia was due, in essence, to failure of renal conservation of potassium.[1]

Cardiovascular functions were observed while the patient was taking therapeutic doses of potassium chloride and during periods of marked restriction of potassium intake, the latter hereafter being referred to as "acute depletion."

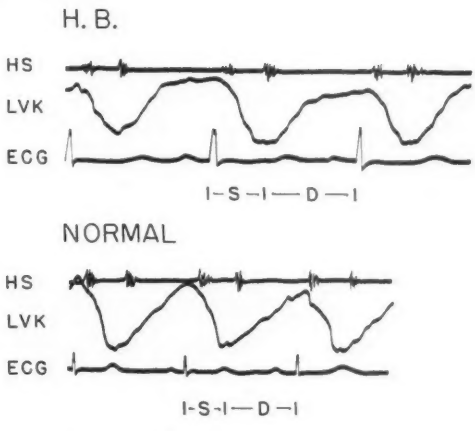


FIG. 2. Diastolic plateau in the left ventricular electrokymogram (*LVK*) (recorded at the mid-point of the left ventricular border) in patient H. B. compared with a normal tracing. Heart sounds (*HS*); electrocardiogram (*ECG*). Retracings from original record.

Orthodiagraphy. Frequent fluoroscopic examinations with orthodiagraphy showed a frontal cardiac area 30 per cent below the predicted normal and a normal silhouette of the heart. During a metabolic balance study in April 1952, diaphragmatic elevation and weakness were detected by fluoroscopy after 3½ days of acute reduction of potassium intake (fig. 1). The serum potassium concentration was then between 1.4 and 1.2 mEq./L. Muscle weakness in the limbs had already been present for 1½ days. The diaphragmatic level at the end of quiet expiration was higher than normal, and the excursion of the diaphragm was reduced. The next day, the acute depletion period was ended by the intravenous and oral administration of potassium chloride. Three hours later the patient felt much better, muscle power improved in the limbs, and the diaphragm returned to its normal level.

Electrokymography. Electrokymographic tracings of the movement of the patient's lower left ventricular border were made.* The typical tracing in figure 2 was recorded in the chronic

* Courtesy of Dr. Peter Kuo, Robinette Foundation, Hospital of the University of Pennsylvania.

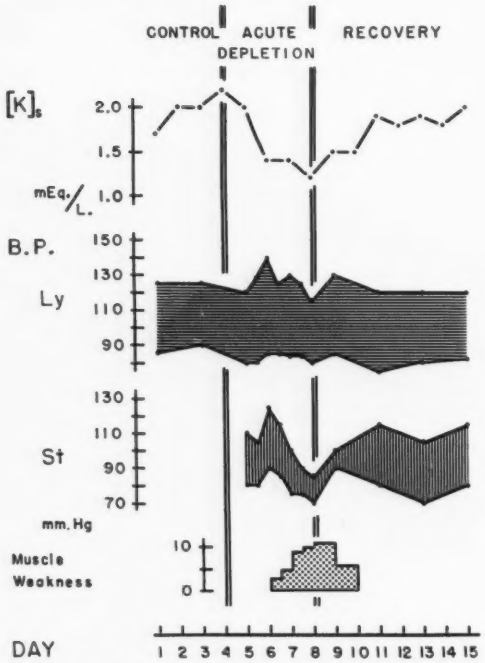


FIG. 3. Relations of serum potassium level ($[K]s$), blood pressure while lying (Ly) and standing (St), and muscle weakness during acute depletion of potassium and in recovery.

hypokalemic state under potassium chloride therapy when the serum potassium was slightly over 2.0 mEq./L. The movement of the left ventricular border was so small that much higher amplification was necessary than usual. The notable abnormality in form was the diastolic plateau. During a period of sharp reduction of potassium intake, a curve resembling a sine wave of very low amplitude was recorded just before the patient fainted.

Heart Sounds. The patient's heart sounds were usually soft, particularly the first. Occasionally, a grade 1 or 2 blowing systolic murmur was heard at the apex and along the medial portions of the fourth and fifth left interspaces. During acute depletion of potassium, the sounds became louder and the systolic murmur increased to grade 3.

Postural Hypotension. The patient's blood pressure varied little from 125/85 during the 4 years of study. During the potassium deprivation study of April 1952, the postural response of the blood pressure was examined. The blood pressures at 1-minute intervals after 5 to 10 minutes rest in recumbency were usually within 5 mm. Hg of 125/85. In the standing position, the systolic pressure fell markedly. The amount of fall increased as the potassium depletion increased; with resumption of usual potassium intake, the fall diminished. Persistent falls in the diastolic pressure also occurred in the acute depletion period. The patient felt lightheaded during the postural hypotension, but did not faint. The postural changes in pressure correlate well in time with changes in serum potassium concentration and muscle strength (fig. 3).

Ballistocardiography. Ballistocardiographic tracings were normal in form. The amplitude of the I–J complex has been about 40 per cent below average for a subject of his age and sex, but within the normal range.

Consecutive tracings during metabolic study were made in October 1952, when the usual potassium intake was withdrawn for 2 days. The tracings were made before lunch and after the subject had rested on the Starr ballistocardiographic table for at least 10 minutes. Amplitude was expressed in Starr's[2] term of "cardiac force" with a slight change in the Starr formula.* The tracings showed no changes in form. The amplitude showed a marked increase in the recovery period following the acute depletion period of 2 days (fig. 4).

Other Studies. The venous pressure and circulation times (Decholin, arm to tongue) were normal in both the control and acute depletion periods.

Electrocardiography. Limb and CR leads of electrocardiograms were recorded in the supine position once or twice a day throughout the study of April 1952, in the control, acute depletion, and recovery periods.

Heart rates taken from the electrocardiograms were resting values in that the tracings were taken under basal conditions in bed, be-

* In this modification, "cardiac force" = $\sqrt{\frac{2(I+J)}{n}}$ where $(I + J)$ is the sum of the $I + J$ wave amplitude (mm.) in all complexes of one or more respiratory cycles and n is the number of complexes measured.

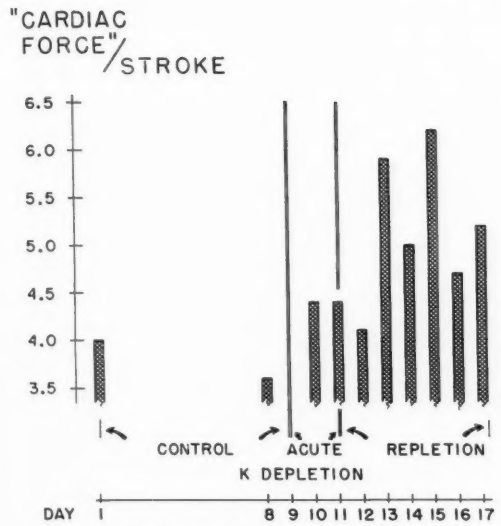


FIG. 4. Ballistocardiographic amplitude expressed in terms of "cardiac force," increased during recovery from acute potassium depletion.

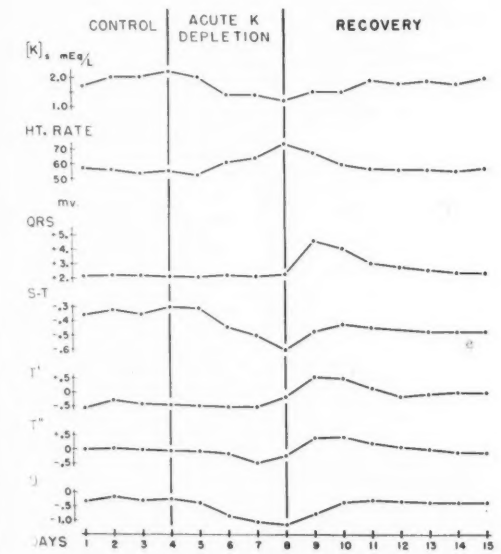


FIG. 5. Changes in serum potassium level ($[K]s$), resting heart rates, and in magnitude of various electrocardiographic variables (in mv.) during a metabolic study of acute potassium depletion.

QRS represents sum of major downward deflections in the *QRS* complexes of leads I and III. *S-T*, *T'*, *T"*, and *U* represent levels of S-T junction and the amplitudes of the 2 T-wave components and of the U wave, relative to the Q junction in CR_4.

fore breakfast. The basal heart rates rose during acute depletion of potassium and fell to control levels during the recovery period (fig. 5).

The QRS complex was unchanged in the acute depletion period, but in the early part of the recovery period, a "left axis shift" developed and the S wave deepened in the medial chest leads (fig. 6). The sum of the major downward deflection of the QRS complex in leads I and III increased and regressed with the "left axis shift" (fig. 5).

The usually depressed S-T segments were depressed further during acute potassium depletion and returned toward the control level in the recovery period (fig. 5).

In the patient's usual state, with the serum potassium about 2.0 mEq./L., the T waves were of low amplitude and either positive or diphasic and there was often a small negative U wave in the precordial leads (fig. 6). Late during acute depletion, the T wave developed a double positive peak with a slight increase in amplitude and the U wave deepened and broadened, reaching beyond the succeeding P wave. In the early part of the recovery period,

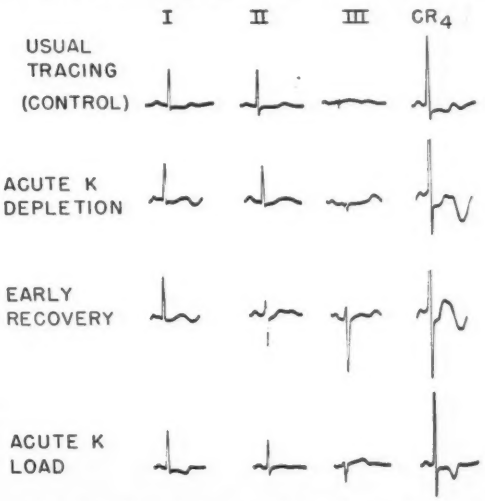


FIG. 6. Retraced electrocardiograms from the limb leads and CR_4 showing characteristic patterns in the patient's usual chronic hypokalemic state (control), at the height of acute potassium depletion, early in recovery, and after a large oral dose of KCl. In the 3 lower tracings from CR_4, the full amplitude of *R* is not included.

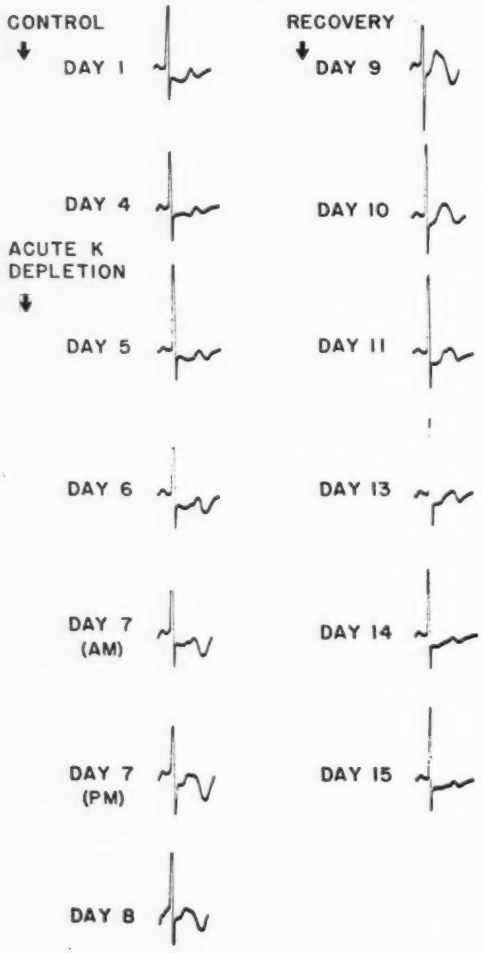


FIG. 7. The complete evolution of CR_4 during a metabolic study of acute potassium depletion (also see fig. 5). The full amplitude of R is not included in all tracings.

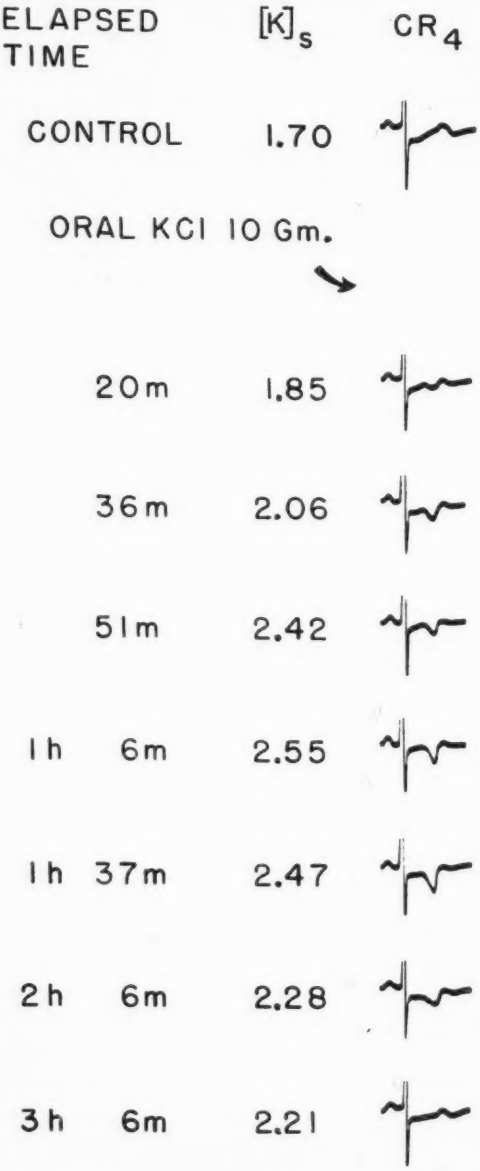


FIG. 8. The evolution of CR_4 after an oral dose of 10 Gm. of potassium chloride.

the T wave became taller, while the deep negative U wave began to regress; by the end of the recovery period, both waves reverted to their previous form (fig. 7).

When a large oral dose of potassium chloride was given to raise the serum potassium to a higher than usual level, a deep negative T wave developed (fig. 8).

DISCUSSION

The cardiovascular abnormalities appear to be attributable solely to the potassium depletion. In analysis, 2 problems can be considered: the mode of production of these changes by the depletion and how well the cardiovascular abnormalities indicate the severity of the depletion. To consider the first

problem, the abnormalities can be taken up individually.

Heart Sounds. Systolic murmurs in association with hypokalemia have been described[3-11] but the complexity of the cases has obscured any direct relationship. Frenkel[11] reported a case with severe hypokalemia in which "high output failure" with a rapid circulation time was a possible explanation for a systolic murmur. Our subject, H. B., however, showed no signs of failure and his circulation time was normal. His systolic murmur and its increase in loudness during acute depletion remain unexplained.

The Electrokymogram. The notable abnormality in the electrokymogram was the diastolic plateau (fig. 4). This feature has been recorded previously from hearts with marked bradycardia (as in complete heart block) where left ventricular filling is completed relatively early in a long diastole and from hearts with constrictive pericarditis where an external restraint to left ventricular expansion exists.[12-14]

No evidence of pericardial disease could be demonstrated in our patient and the tracing in figure 4 was recorded at a heart rate of 68/min. Considered speculatively, the limitation of the outward movement of the left ventricular wall early in diastole may arise from an abnormality in the elastic properties of the myocardium itself. The first possible abnormality is diffuse and microscopic scarring following focal necrosis, a known consequence of chronic potassium depletion.[15-19] A second possible abnormality is a functional resistance of the myocardium to distention beyond a certain point. Pertinent in this regard are the decrease in diastolic size of the frog ventricular muscle as potassium and sodium are lost[20] and the increased diastolic tone of frog heart in Ringer's solution with a low concentration of potassium.[21]

The Ballistocardiograph. The cause of the increased ballistocardiographic amplitude in the recovery period is unknown. Attempts to correlate ballistic amplitude with ionic and fluid shifts were fruitless.[1] In the only previous report of increase in ballistic amplitude in association with major ionic and fluid shifts, Jones[22] found maximal amplitude during diureses in cardiac patients, instead of after the major fluid and ionic shifts as found in this study.

Postural Hypotension. Postural hypotension was reported by Earle and co-workers[3] in association with chronic hypokalemia. In our patient the blood pressure was usually normal. The postural hypotension developed and regressed with the fall and return of the serum potassium level and with the appearance and disappearance of muscle weakness in the limbs (fig. 3). Three mechanisms might account for the postural hypotension:

1. Reduced muscle tone. The muscle weakness in the legs might lower tissue pressure against the leg veins and lead to pooling of blood in the legs during standing.

2. Reduced peripheral vascular reactivity. Rats kept on a diet deficient in potassium develop hypotension[23] in close relation to the serum potassium concentration.[24] This effect may be related to a lessened response of peripheral vessels to pressor substances.[25] In a patient with marked hypokalemia during recovery from diabetic acidosis "high-output failure" was ascribed to decreased peripheral resistance.[11] The postural hypotension developed by our patient might be attributable in part to a failure of vascoconstriction in leg vessels in response to standing.

3. During the entire period of acute potassium depletion, the patient was in a state of mild hyperventilation, manifest by tachypnea and a rise in pH and fall in CO_2 content of the arterialized cutaneous blood. It is suggested that hyperventilation, arising from anxiety due to the increasing muscle weakness or stimulated by intracellular acidosis in the respiratory center,[26] could contribute to the postural fall in pressure.[27-29]

Neither the serum sodium level nor the calculated blood volume changes correlated satisfactorily with the postural blood pressure changes.

Electrocardiography. During the 4-year study of patient H. B., with serum potassium level between 1.8 and 2.8 mEq./L., the tracings always showed S-T segment depression and T-U wave alterations (fig. 6).

The moderate bradycardia of 50 to 55 beats/

TABLE 1.—*Correlation of Electrocardiographic and Metabolic Data: Regression Equations, Correlation Coefficients (r), and Significance (p).*

	r	p Value
Resting heart rate:		
With serum potassium level:		
Rate = 88 − 16 $[K]_s$	−0.83	<0.001
With arterial cutaneous blood CO_2:		
Rate = 171 − 5.6 $[CO_2]_{ACB}$	−0.91	<0.001
S-T segment level (CR_4):		
With serum potassium level:		
S-T segment level = 0.214 $[K]_s$ − 0.80	+0.76	<0.01
With cumulative K balance:		
With S-T segment level = 0.00042 (Cum. K Bal.) − 0.34	+0.79	<0.01
U-Wave amplitude (CR_4):		
With serum potassium level:		
U amplitude = 0.85 $[K]_s$ − 1.96	+0.83	<0.001
Cumulative potassium balance:		
With serum potassium level	+0.47	<0.2 >0.1

Note:

$[K]_s$ = serum potassium level in mEq./L.

$[CO_2]_{ACB}$ = arterialized cutaneous blood CO_2 content in mM/L.

S-T segment level = depression of S junction below Q junction in mv.

Cumulative K balance is in total mEq. of external balance. U-wave amplitude is measured relative to the Q junction, in mv.

min. during the control period of the April 1952 metabolic study (fig. 5) is consistent with the previous findings of bradycardia during chronic potassium depletion in young rats[30] and chicks[31] and in human beings,[17, 32, 33] though it may simply be a normal rate for this patient. The more rapid rates in the acute depletion period (fig. 5) have a parallel in the rising rates in dogs during the development of acute total body potassium deficit (by extracorporeal dialysis),[34] and of acute severe hypokalemia in human beings.[35-38]

The changes in the QRS complex, the "left axis shift," were similar to those observed by Weller[34] in dogs that underwent dialysis. The time sequence differed in that these changes in our patient came at the beginning of the recovery period when the serum potassium had begun to rise even though estimated intracellular repletion had not begun, whereas in the dogs of Weller the changes developed during the withdrawal of potassium from the intracellular compartment while the serum level was constant. The potassium concentration changes accompanying the QRS alteration in both the patient and the dogs would be expected to lead to a rise in the ratio of extracellular-intracellular myocardial concentrations of potassium; such a change in ratio may be a common denominator in both observations. It must be stated that minor changes in heart position as the tracings were taken from the patient in the supine position may have been responsible for the QRS changes. The time sequence of the T-wave changes closely paralleled that of the QRS changes (fig. 5).

The changes in the level of the S-T segment (or more precisely, the S junction) in CR_4 relative to the Q junction were found to correlate equally well with the serum potassium level and the cumulative potassium balance (table 1). From these correlations it is not possible to pick out a certain causal basis for the S-T segment shifts. In the narrow range of heart rates observed, 53–74, the S-T segment shifts cannot be attributed reasonably to rate changes. The findings of Weller[34] in dogs that the S-T segment depressions, developing during depletion of potassium, persisted when the serum level of potassium was raised rapidly by infusion of potassium, suggested that the S-T shifts might be closely related to a continuing myocardial depletion of intracellular potassium. A similar situation was present in patient H. B., in that the S-T segment level did not return completely to control levels during the recovery period (fig. 5). In this period the cumulative negative balance of intracellular potassium persisted (−300 to 400 mEq.) even though the serum potassium level returned to control levels (table 1).* With more investigation of this problem, the

* The failure of intracellular repletion of potassium in the recovery period when the serum potassium level returned to control level accounted for the poor correlation between the 2 variables. The partial return of the S-T segment toward control levels accounts for its satisfactory correlation with both metabolic variables.

S-T segment depression may be found to be a useful guide to the magnitude of cellular potassium depletion.

In the preceding discussion the repolarization waves were arbitrarily named T and U waves. Other possibilities in nomenclature for these waves were considered: 1. The first 2 waves forming a double positive peak as T waves, and the following negative wave as U wave. 2. The first positive peak as T, the second positive peak as U, and the negative wave as V wave. 3. The first positive peak as T wave of the atrium (with markedly prolonged P-Ta interval), the second positive peak as T wave of the ventricle, and the negative wave as U wave. Evidence for the last 2 possibilities was insufficient, so the first conventional nomenclature was used. On this basis, measurements of the interval from Q to either apex of T showed a prolongation as judged by the criteria of Surawicz and Lepeschkin.[39] This prolongation occurred without the presence of hypocalcemia.

The T waves did not show the expected further lowering and inversion during the acute depletion study but became more positive early in the recovery period (fig. 7). This sequence is not so unusual if the deeply inverted T wave present at higher serum potassium levels (fig. 8), possibly reflecting myocardial tissue damage,[15-18] represents the patient's "normal" T wave. If so, the positive T waves after acute depletion may be simply following a general rule of change of polarity with acute potassium depletion. Additional evidence for this view was found in the tracings of a potassium-depleted patient studied by McAllen.[19] No explanation could be devised for the delay in the appearance of the major part of the T wave change until the early recovery period (fig. 5); it may be pertinent that Schwartz[40] found that pattern changes in potassium depletion often appeared to lag behind changes in the total balance of potassium.

It is readily seen (fig. 5) that the T waves of this patient did not correlate with changes in the serum level of potassium, as the behavior of the T wave during the acute loading of potassium further emphasizes. Figure 8 shows that when the potassium serum level was 2.06 mEq./L. and rising, the pattern was identical to that seen when the serum level was 2.28 mEq./L. and falling. Therefore the T-wave pattern in this patient must be related to an aspect of electrolyte distribution in the heart not reflected by balance data or serum potassium level; nevertheless, attempts to provide evidence for this hypothesis by calculating estimated intracellular:extracellular ratios for potassium during the T-wave changes were fruitless.

The amplitude of the negative U waves (CR_4) showed a good correlation with the serum potassium level (fig. 5, table 1). The change in amplitude of U waves paralleled the changes in the S-T segment level (CR_4) and did not parallel the T-wave changes (fig. 5).

As has been mentioned, attempts to relate electrocardiographic variables to calculated total body intracellular concentrations of sodium and potassium and intracellular and extracellular concentration ratios have been unrewarding. In view of ignorance as to how closely total body external and internal balances of sodium and potassium can be relied on to reflect changes in the intracellular concentrations of these ions in the myocardium, this failure is not surprising.

The remaining problem is whether it is possible to estimate the magnitude of the chronic potassium depletion in this patient from the cardiovascular phenomena. The number of studies relating the development of cardiovascular disturbances to the degree of potassium depletion is small, if only those giving satisfactory quantitative information are considered.

Black and Milne[26] depleted 2 normal subjects of potassium with a low potassium diet. In 1 subject with a total depletion of 280 mEq. K^+ and a minimal serum potassium level of 3.2 mEq./L., no electrocardiographic changes were seen. A second subject developed a U wave in lead II with a potassium depletion of 270 mEq. K and a serum level of 3.0 mEq./L. The subject of Blahd and Bassett[41] reached a potassium deficit of 270 mEq. and a minimal serum potassium level of 3.0 mEq./L. in 55 days on a low potassium diet; he showed no changes in

TABLE 2.—*Relation of Size of Potassium Depletion in Normal Experimental Subjects to Electrocardiographic Changes*

Size of K depletion	Type of electrocardiogram	
	Changes attributable to K depletion	No Changes attributable to K depletion
	%	%
<100 mEq.	15	30
100–200 mEq.	20	30
200–300 mEq.	15	30
>300 mEq.	50	10
Total	100	100

Size of K depletion determined by balance studies. Changes attributable to potassium depletion include characteristic changes in S-T segment level, and in T and U-wave contour and amplitude. Data[26, 40-42, 45, 46] adjusted for size of samples and percentages rounded to nearest 5 per cent.

blood pressure or in electrocardiographic tracings. Three of 4 normal medical students on low potassium diets developed total potassium depletions of 116 to 195 mEq. over 7 to 8 days, with minimal serum potassium levels of 3.5 mEq./L.[42] None of these 3 showed changes in reclining and standing blood pressure, in electrocardiographic patterns, or in form of ballistocardiographs. The fourth developed small increases in the amplitude of a normal positive U wave during a depletion of 300–400 mEq. with a serum level of 3.1–2.8 mEq./L. Schwartz and associates[40] studied the relation between electrocardiographic changes and the magnitude of potassium depletion in subjects in whom potassium loss was induced by adrenocortical hormones, acidifying salts, and excessive use of laxatives. They could not find a distinct correlation between the negative potassium balance and the changes in the electrocardiograms that were characteristic of potassium depletion. Fourman[44] induced potassium depletion in 2 normal subjects by feeding an ion-exchange resin. Despite the production of extracellular acidosis by the resin and the tendency of metabolic acidosis to mask the electrocardiographic patterns of potassium depletion,[43] electrocardiographic tracings with characteristics attributable to potassium depletion were found in 2 experiments on 1 subject with depletions of 338 and 839 mEq. In studies by Womersley and Darragh[45] potassium depletions of 330, 266, and 162 mEq. were reached by normal subjects with low potassium diets without the development of electrocardiographic changes.

The data from these studies have been arranged in table 2 to show the relationships between electrocardiographic tracings of the hypokalemic type and the magnitude of the potassium depletion. They suggest that patient, H. B., showing chronically a hypokalemic-type tracing, has a 65 per cent chance of having a chronic potassium depletion of at least 200 mEq., and a 50 per cent chance of a depletion greater than 300 mEq. When the additional depletion of 374 mEq. attained acutely in the April 1952 study is added to the estimate, the depletion accompanying the appearance of the postural hypotension may have reached a minimum of 600 to 700 mEq.

SUMMARY

A male adult with intermittent muscular paralysis was found to have a chronic hypokalemia due to failure of renal conservation of potassium.

Diaphragmatic elevation and diminished excursion were observed fluoroscopically during an acute potassium depletion study.

The motion of the left ventricular border as recorded in the electrokymograph showed low amplitude and a diastolic plateau, possibly due to patchy fibrosis in the myocardium as a consequence of chronic potassium depletion, or a functional change in the elastic properties of the myocardium.

A mild postural hypotension developed during acute reduction of the potassium intake, possibly caused by reduction in leg muscle tone, reduced peripheral vascular resistance, and a background of hyperventilation.

Increases in ballistocardiographic wave amplitude were found during recovery from an acute potassium depletion study.

The changes in resting heart rate, S-T segment level, and U wave amplitude correlated closely with changes in the serum potassium level. The S-T segment level also correlated

well with the cumulative potassium balance, even though the correlation between the cumulative potassium balance and the serum potassium level was not good.

The time sequence of development and regression of a "left axis shift" in the QRS complex paralleled changes in amplitude of the T wave. These changes could not be correlated with metabolic variables.

Comparison of the cardiovascular findings in this patient with those in normal subjects depleted of potassium in several ways suggests that the patient had a minimal chronic potassium depletion of 300 mEq. and reached a depletion of at least 700 mEq. during a marked reduction in his potassium intake.

Acknowledgment

We wish to thank Dr. J. Russell Elkinton for his generous support during this study. He, Drs. A. G. Hills, C. F. Kay, I. Starr, C. C. Wolferth, F. C. Wood, and Miss Elizabeth Trotter kindly gave us thorough and useful criticism of the manuscript.

Summario in Interlingua

Esseva constatate, in un masculo adulte con intermittente paralyse muscular, le presentia de chronic hypokalemia debite a non-conservation renal de kalium.

Elevation diaphragmatic e excursion diminuite esseva observate fluoroscopicamente durante un studio de acute depletion de kalium.

Le motion del margine sinistro-ventricular, registrate in le electrokymographo, monstrava un basse amplitude e un plateau diastolic, possibilemente debite a placas de fibrosis in le myocardio (disveloppate in consequentia de chronic depletion de kalium) o a un alteration functional del qualitates elastic del myocardio.

Se disveloppava un leve hypotension postural durante acute reduction del ingestion de kalium, possibilemente causate per reduction del tono muscular del gambas, reducite resistentia periphero-vascular, e un fundo de hyperventilation.

Augmentos del amplitude in le undas ballistocardiographic esseva constatate durante le recovramento ab un studio de acute depletion de kalium.

Le alterationes del frequentia cardiac in stato de reposo, del nivello del segmento S-T, e del amplitude del unda U esseva nettemente correlationate con alterationes in le nivello del kalium seral. Le nivello del segmento S-T monstrava etiam un bon correlation con le balancia de kalium cumulative, ben que le correlation del balancia de kalium cumulative con le nivello de kalium seral non esseva bon.

Le sequentia temporal del disveloppamento e del regression de un "displaciamento sinistro-axial" in le complexo QRS esseva parallel a alterationes de amplitude in le unda T. Iste alterationes non esseva correlationabile con variabiles metabolic.

Le comparation del constatationes cardiovascular in iste patiente con correspondente constatationes in subjectos normal con depletion de kalium effectuate in varie manieras pare indicar que le patiente habeva un minimal depletion chronic de kalium de 300 mEq e que ille attingeva un depletion de 700 mEq o plus durante un marcate reduction del ingestion de kalium.

REFERENCES

1. Squires, R. D., and Huth, E. J.: A patient with chronic hypokalemia. II. Metabolic and renal function studies. In preparation.
2. Starr, I., Horwitz, O., Mayock, R. L., and Krumbhaar, E. B.: Standardization of the ballistocardiogram by simulation of the heart's function at necropsy; with a clinical method for the estimation of cardiac strength and normal standards of it. Circulation **1:** 1073, 1950.
3. Earle, D. P., Sherry, S., Eichna, L. W., and Conan, N. J.: Low potassium syndrome due to defective renal tubular mechanisms for handling potassium. Am. J. Med. **11:** 283, 1951.
4. Biemond, A., and Daniels, A. P.: Familial periodic paralysis and its transition into spinal muscular atrophy. Brain **57:** 91, 1934.
5. Pudenz, R. H., McIntosh, J. F., and McEachern, D.: The role of potassium in familial periodic paralysis. J.A.M.A. **111:** 2253, 1938.
6. Stewart, H. J., Smith, J. J., and Milhorat, A. T.: Electrocardiographic and serum potassium changes in familial periodic paralysis. Am. J. M. Sc. **199:** 789, 1940.
7. Gamble, A. H., Wiese, H. F., and Hansen, A. E.: Marked hypokalemia in prolonged diarrhea; possible effect on heart. Pediatrics **1:** 58, 1948.
8. Marks, L. J.: Potassium deficiency in surgical patients. Ann. Surg. **132:** 20, 1950.

[9] LANS, H. S., STEIN, I. F., JR., AND MEYER, K. A.: Diagnosis, treatment, and prophylaxis of potassium deficiency in surgical patients; analysis of 404 cases. Surg. Gynec. & Obst. **95:** 321, 1952.

[10] HALL, R. J., AND SHERMAN, J. L., JR.: Significance of potassium depletion in poliomyelitis. Am. J. Med. **14:** 124, 1953.

[11] FRENKEL, M., GROEN, J., AND WILLEBRANDS, A. F.: Low serum potassium level during recovery from diabetic coma. Arch. Int. Med. **80:** 728, 1947.

[12] AKMAN, L. C., MILLER, A. J., SILBER, E. N., SCHACK, J. A., AND KATZ, L. N.: The ventricular electrokymogram. Circulation **2:** 890, 1950.

[13] GILLICK, F. G., AND REYNOLDS, W. F.: Electrokymographic observations in constrictive pericarditis. Radiology **55:** 77, 1950.

[14] MCKUSICK, V. A.: Chronic constrictive pericarditis. II. Electrokymographic studies and correlations with roentgenkymography, phonocardiography, and right ventricular pressure curves. Bull. Johns Hopkins Hosp. **90:** 27, 1952.

[15] FOLLIS, R. H., JR., ORENT-KEILES, E., AND MCCOLLUM, E. V.: The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. Am. J. Path. **18:** 29, 1942.

[16] PERKINS, J. G., PETERSEN, A. B., AND RILEY, J. A.: Renal and cardiac lesions in potassium deficiency due to chronic diarrhea. Am. J. Med. **8:** 115, 1950.

[17] KEYE, J. D., JR.: Death in potassium deficiency; report of a case including morphologic findings. Circulation **5:** 766, 1952.

[18] KORNBERG, A., AND ENDICOTT, K. M.: Potassium deficiency in the rat. Am. J. Physiol. **145:** 291, 1946.

[19] MCALLEN, P. M.: Myocardial changes occurring in potassium deficiency. Brit. Heart J. **17:** 5, 1955.

[20] HAJDU, S.: Mechanism of staircase and contracture in ventricular muscle. Am. J. Physiol. **174:** 371, 1953.

[21] SPEALMAN, C. R.: The action of ions on the frog heart. Am. J. Physiol. **130:** 729, 1940.

[22] JONES, R. J.: The Nickerson ballistocardiogram in arteriosclerotic heart disease with and without congestive failure. Circulation **6:** 389, 1952.

[23] FREED, S. C., AND FRIEDMAN, J.: Hypotension in the rat following limitation of potassium intake. Science **112:** 788, 1950.

[24] ST. GEORGE, S. M., FREED, S. C., AND ROSENMAN, R. H.: Correlation of serum potassium concentrations with the blood pressure in rats fed a potassium-deficient ration. Circulation **6:** 371, 1952.

[25] ROSENMAN, R. H., FREED, S. C., AND FRIEDMAN, J.: The peripheral vascular reactivity of potassium-deficient rats. Circulation **5:** 412, 1952.

[26] BLACK, D. A. K., AND MILNE, M. D.: Experimental potassium depletion in man. Clin. Sc. **11:** 397, 1952.

[27] BROWN, E. B., JR.: Physiological effects of hyperventilation. Physiol. Rev. **33:** 445, 1953.

[28] ENGEL, G. L., ROMANO, J., AND MCLIN, T. R.: Vasodepressor and carotid sinus syncope. Arch. Int. Med. **74:** 100, 1944.

[29] BURNUM, J. F., HICKAM, J. B., AND MCINTOSH, H. D.: The influence of hypocapnia on arterial blood pressure; clinical significance in orthostatic hypotension. Clinical Research Proceedings **1:** 39, 1953.

[30] PEARSON, O. H., HASTINGS, A. B., CURRENS, J. H., AND WHITECOMB, F. D.: Electrocardiographic changes in potassium-deficient rats. Conference on Metabolic Aspects of Convalescence, Transactions of the Seventeenth Meeting, Josiah Macy, Jr. Foundation, New York, 1948, p. 54.

[31] STURKIE, P. D.: Abnormal electrocardiograms of chickens produced by potassium deficiency and effects of certain drugs on the abnormalities. Am. J. Physiol. **162:** 538, 1950.

[32] KJERULF-JENSEN, K., KRARUP, N. B., AND WARMING-LARSEN, A.: Persistent hypokalemia requiring constant potassium therapy. Lancet **1:** 372, 1951.

[33] ELLISON, H. S., AND HOLLEY, H. L.: Hypokalemia due to insufficient dietary intake; two cases with presenting respiratory symptoms. Am. Pract. **4:** 6, 1953.

[34] WELLER, J. M., LOWN, B., HOIGNE, R. V., WYATT, N. F., CRISCITIELLO, M., MERRILL, J. P., AND LEVINE, S. A.: Effects of acute removal of potassium from dogs. Changes in the electrocardiogram. Circulation **11:** 44, 1955.

[35] HOLLER, J. W.: Potassium deficiency occurring during the treatment of diabetic acidosis. J.A.M.A. **131:** 1186, 1946.

[36] LOGSDON, C. S., AND MCGAVACK, T. H.: Death, probably due to potassium deficiency, following control of diabetic coma. J. Clin. Endocrinol. **8:** 658, 1948.

[37] STEPHENS, F. I.: Paralysis due to reduced serum potassium concentration during treatment of diabetic acidosis; report of case treated with 33 grams of potassium chloride intravenously. Ann. Int. Med. **30:** 1272, 1949.

[38] DIEFENBACH, W. C. L., FISK, S. C., AND GILSON, S. B.: Hypopotassemia following bilateral ureterosigmoidostomy. New England J. Med. **244:** 326, 1951.

[39] SURAWICZ, B., AND LEPESCHKIN, E.: The electrocardiographic pattern of hypopotassemia with and without hypocalcemia. Circulation **8:** 801 1953.

[40] SCHWARTZ, W. B., LEVINE, H. D., AND RELMAN,

A. S.: The electrocardiogram in potassium depletion. Its relation to the total potassium deficit and the serum concentration. Am. J. Med. **16:** 395, 1954.

[1] BLAHD, W. H., AND BASSETT, S. H.: Potassium deficiency in man. Metabolism **2:** 218, 1953.

[2] SQUIRES, R. D., AND HUTH, E. J.: The renal conservation of potassium in man. In preparation.

[3] ROBERTS, K. E., AND MAGIDA, M. G.: Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate, and sodium as compared with those produced by an increase in potassium. Circulation Research **1:** 206, 1953.

[44] FOURMAN, P.: Depletion of potassium induced in man with an exchange resin. Clin. Sc. **13:** 93, 1954.

[45] WOMERSLEY, R. A., AND DARRAGH, J. H.: Potassium and sodium restriction in the normal human. J. Clin. Invest. **34:** 456, 1955.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Adams-Stokes Disease. Robert Adams (1791–1875), one of the surgeons to Jervis Street Infirmary, Dublin, described "Cases of Diseases of the Heart, Accompanied with Pathological Observations" in the *Dublin Hospital Reports* 4: 353–453, Dublin, 1827. On page 391 appears the following:

"Feburary 20, 1822, I was called to visit a gentleman in my neighborhood, aged fifty years, who had suddenly fallen down, as reported to me, in an apoplectic fit. I found him in a state of complete insensibility; his face (naturally pale and sickly) was now red and bloated; his breathing stertorous, with a slow pulse. . . . In the last year he had two apoplectic attacks, exactly resembling that which I had just witnessed: from these he recovered without any paralysis of the muscles. . . .

"An officer in the revenue, aged sixty-eight years, of a full habit of body, had for a long time been incapable of any exertion, as he was subject to oppression of his breathing and continued cough. In May 1819 . . . I saw this gentleman: he was just then recovering from the effects of an apoplectic attack, which had suddenly seized him three days before. . . . What most attracted my attention was, the irregularity of his breathing, and remarkable slowness of the pulse, which generally ranged at the rate of 30 in a minute. . . . [During seven years he had been seen] in not less than twenty apoplectic attacks . . . He would then fall down in a state of complete insensibility . . . his pulse wold become even slower than usual. . . . He recovered from these attacks without any paralysis. . . . In both these cases . . . apoplexy must be considered less a disease in itself than symptomatic of one, the organic seat of which was in the heart."

William Stokes (1804–1878) in his article "Observations on Some Cases of Permanently Slow Pulse" which appeared in the *Dublin Quarterly Journal of Medical Science* 2: 73–85 (August 1), 1846, refers to these case histories as follows:

"In the fourth volume of the Dublin Hospital Reports, Mr. Adams has recorded a case of permanently slow pulse, in which the patient suffered from repeated cerebral attacks of an apoplectic nature, though not followed by paralysis. The attention of subsequent writers on diseases of the heart, has not been sufficiently directed to this case, which is an example of a very curious and, as there is reason to believe, special combination of symptoms."

Significance of Abnormal Phase II Response to Valsalva Maneuver in Cardiac Patients

By ROBERT W. BURROUGHS, M.D., AND ROBERT A. BRUCE, M.D.

Abnormal responses to a standardized Valsalva maneuver have been proposed as additional criteria for heart failure. The present study was undertaken to determine the variability of these responses in normal subjects as well as frequency of abnormal responses in cardiac patients. Only phase II responses could be considered reliable for this purpose. Discrepancies between phase II responses were observed in relation to other criteria.

VARIOUS effects of forced expiration against a closed glottis (Valsalva maneuver) have been recognized, virtually since ancient times.[1] Abnormal responses in patients with heart failure have been observed recently by Elisberg and colleagues[2] and by Judson, Hatcher, and Wilkins.[3] Indeed Sharpey-Schafer[4] has suggested the use of the Valsalva maneuver as another method of evaluating cardiac patients with respect to heart failure.

For purposes of analysis, the several responses of Valsalva maneuver (hereafter designated as Vm) were separated into 4 phases by Hamilton, Woodbury, and Harper,[5] as follows: (fig. 1)

I. The blood pressure initially rises with a slight increase in pulse pressure. II. A fall in blood pressure, smaller pulse pressure, and acceleration of the heart rate ensue. As this phase continues, mean blood pressure may turn upward. III. As the strain is abruptly discontinued, blood pressure falls precipitously. IV. Post-Vm systolic, diastolic, and pulse pressures quickly rise; bradycardia may result. Subsequent studies during cardiac catheterization[2, 3] have shown elevated right atrial, right ventricular, and pulmonary arterial pressures during the strain with a less conspicuous pulmonary arterial post-Vm overshoot.

Patients with manifestations of heart failure in contrast, according to Sharpey-Schafer, maintain the strain (phase II) pulse pressure without a post Valsalva (phase IV) diastolic pressure overshoot (fig. 2). ("Failure response" of Judson and co-workers.)

The present study of 19 control subjects and 44 patients with heart disease was undertaken to assess validity and limitations of the Vm as an ancillary method for diagnosis of cardiac insufficiency.

The latter was evaluated by clinical criteria of appropriate symptoms and physical signs, estimation of functional capacity (according to criteria of New York Heart Association) and, in addition, objectively by means of a standard exercise tolerance test in 25 of these patients.

MATERIAL AND METHODS

The 19 control subjects included 4 healthy physicians and 15 ambulatory patients ranging in age from 19 to 64, with a median of 39 years. These patients were hospitalized for miscellaneous diseases but none had either heart or pulmonary disease. Forty-four selected patients with heart disease ranged in age from 12 to 79, with a median of 46 years. Three of the controls and 14 of the cardiac patients were women. Twenty-nine of the patients had rheumatic heart disease, 7 had hypertensive or arteriosclerotic heart disease, 4 had congenital heart disease, 2 had cor pulmonale, and 2 had heart disease of uncertain etiology.

Direct brachial, radial, or femoral arterial pressure was recorded with a Statham strain gage and a direct-writing (Sanborn) oscillograph. After a deep inspiration, an intra-oral pressure of 40 mm. Hg (monitored by an aneroid manometer) was sustained for 10 seconds, and then abruptly released. The tracing

From the University of Washington, Seattle, Wash.
Dr. Burroughs was a Trainee of the National Heart Institute, National Institutes of Health, U. S. Public Health Service, 1954–55.

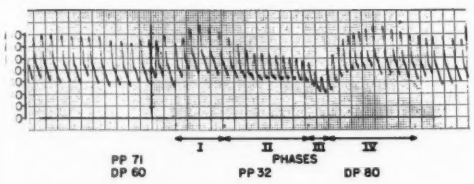


FIG. 1. Four phases of arterial pressure responses to Valsalva maneuver in a normal subject. Ratios A and B were derived from changes in pulse pressure and diastolic pressure. Ratio A = $\frac{(32 - 71) \times 100}{71}$ = −55%, ratio B = $\frac{(80 - 60) \times 100}{60}$ = +33%.

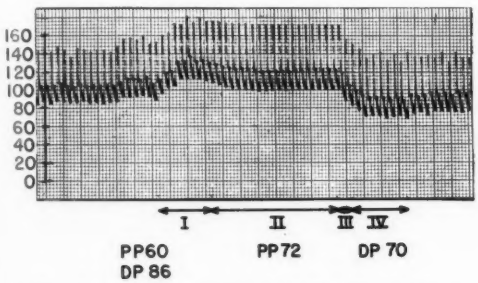


FIG. 2. Abnormal response to Valsalva maneuver observed in a patient with congestive heart failure. Note increased, rather than decreased pulse pressure in phase II. Ratio A = $\frac{(72 - 60) \times 100}{60}$ = +20%, ratio B = $\frac{(70 - 86) \times 100}{86}$ = −19%.

of this standardized Vm was analyzed according to criteria established by Sharpey-Schafer as follows: (figs. 1 and 2)

$$\frac{\text{phase II } PP - \text{pre-Vm } PP \times 100}{\text{pre-Vm } PP} \quad \text{(Ratio A)}$$

$$\frac{\text{phase IV } DP - \text{pre-Vm } DP \times 100}{\text{pre-Vm } DP} \quad \text{(Ratio B)}$$

where, PP = pulse pressure
DP = diastolic pressure

In 15 of the control subjects, 2 successive tracings were analyzed to determine variance.

Twenty-five of the cardiac patients performed a standard exercise tolerance test, walking a 10 per cent grade at 1.73 mph on a motor driven treadmill for 10 minutes if tolerated. The cardiorespiratory performance was expressed in terms of the Physical Fitness

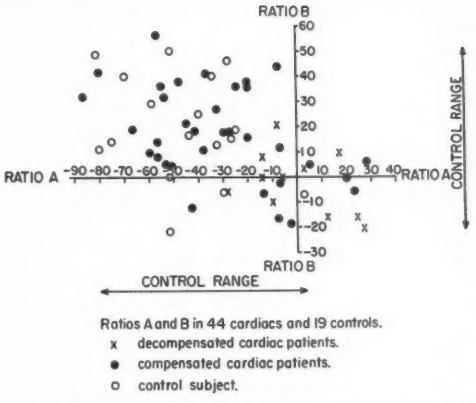


FIG. 3. Ratio A plotted against ratio B in both cardiac patients and normal subjects.

Index (PFI).[6] Normal values average 19 with a range from 13–26.

For purposes of this paper, decompensated patients are defined as those with physical signs of heart failure, such as rales, elevated venous pressure, hydrothorax, hepatomegaly, ascites, or edema. The term compensated implies absence of these signs.

RESULTS

Control Subjects. The mean change of phase II pulse pressure (ratio A) in 19 control subjects was −47 ± 20 per cent, with a range from +3 to −81 per cent (fig. 3). The mean change of phase IV diastolic pressure (ratio B) was +18 ± 19 per cent, with a range from −25 per cent to +51 per cent. The phase II pulse rate was 13 beats per minute higher, on the average than the pre-Vm pulse rate. Contrary to expectations, average of the slowest phase IV pulse rate was only one beat per minute less than the pre-Vm pulse rate.

Analysis of 2 successive Vm determinations in 15 control subjects revealed a coefficient of variation for phase II pulse pressure change (ratio A) of 11 per cent, and for phase IV diastolic pressure change (ratio B) of 40 per cent. Thus, the former ratio was more reproducible than the latter.

Patients. Ratio A deviated by more than 2 σ from mean of control subjects in 10 of 44 patients. Pulse pressure in phase II was essentially maintained or paradoxically increased in each

of these 10 patients. Five had decompensated chronic heart failure, manifested by combinations of rales,[3] increased venous pressure,[5] hepatomegaly, hydrothorax, ascites, or edema.[4] Etiology in 3 of these 5 was rheumatic heart disease, whereas it was hypertensive and arteriosclerotic in 1, and possibly related to hemochromatosis in the last individual.

Of the remaining 5 patients out of 10 with abnormal phase II responses to Vm, 1 had rheumatic heart disease with borderline compensation, 1 had digitalis toxicity and compensated chronic cardiac insufficiency due to rheumatic heart disease, 1 had cyanotic congenital heart disease, 1 had congenital infundibular stenosis, and 1 had an old myocardial infarction.

Seven of the 10 had normal sinus rhythm and 3 had chronic atrial fibrillation.

The mean values for ratios A and B in various subgroups of the 44 cardiac patients are shown in table 1, for comparison with control values. Noteworthy is the maintenance of phase II pulse pressure in the 11 patients with decompensated chronic heart failure, in contrast to 7 patients with borderline compensation, and with 19 control subjects. The criteria failed to discriminate between 9 cardiac patients with a functional capacity of either class I or II, and 17 patients in class III. Phase II responses in 13 patients in class IV were similar to the values obtained in the decompensated patients; actually 8 of the decompensated patients also were included in the class IV group.

Both ratios A and B failed to discriminate between 9 cardiac patients with normal exercise tolerance (mean PFI 19) and 16 cardiac patients with subnormal exercise tolerance (mean PFI 6.3).

The mean phase II response (ratio A) in 1 patients with average circulation time (arm to tongue with decholin) of 14 seconds was −46 per cent. Eight patients with an average circulation time of 39 seconds had a mean ratio of 0 per cent (p .006).

Two patients with cor pulmonale, one decompensated, as well as 2 other patients with pulmonary emphysema not included in this study, had normal Vm responses (mean ratio A −54 per cent, mean ratio B +20 per cent).

Only 2 of the 44 patients had values for ratio B barely deviating from the mean ratio of control subjects by greater than 2 standard deviations.

Discussion

Either maintenance or paradoxic increase of pulse pressure during the strain of a standard Valsalva maneuver (Vm) was associated with manifestations of decompensated heart failure in 5 of 10 patients. Since 4 of the remaining 5

Table 1.—*Evaluation of Results of Standard Valsalva Maneuver*

Group	No.	Incidence of abnormal responses		Ratio A		Ratio B	
		phase II	phase IV	Mean %	Range %	Mean %	Range %
Controls	19	1	1	−47 ±20	+3 −81	+18 ±19	−21 +50
Cardiac patients:							
class I + II	9	1	0	−30	+28 −87	+16	−16 +44
class III	17	3	1	−35	+12 −80	+23	−16 +57
class IV	13	5	1	−3	+27 −33	+3	−20 +27
Compensated	26	4	1	−25	+28 −87	+22	−18 +57
Borderline compensation	7	1	0	−36	+23 −67	+5	−12 +19
Decompensated	11	5	1	0	+27 −30	−3	−20 +21
Normal PFI* (mean 19)	9	2	0	−29	+12 −87	+19	−18 +44
PFI* 6-13	7	1	0	−32	+3 −57	+18	+4 +36
PFI* < 6	9	1	0	−35	+28 −67	+19	0 +36

* PFI = Physical Fitness Index.

with this abnormal response were definitely clinically compensated, it cannot be regarded as diagnostic of decompensated heart failure in all instances. With one exception, the 11 decompensated patients tended to maintain or increase phase II pulse pressure, though the response was statistically abnormal in only 5 of the 11.

Phase I of the Vm in normal subjects is thought to be due in part to forceful evacuation of blood from pulmonary vasculature and left heart.[7] Phase II is related to diminished venous return to the right heart as demonstrated by venography[8, 9] resulting in decreased cardiac output. Abnormal phase II is ascribed by Stucki and associates[9] to reduction of the normal "venous blockade." They describe only slight increases in the circulation times (p 32) from antecubital and femoral veins to the brachial artery *during* the Vm in patients in congestive heart failure, in contrast to the marked delay observed in normal subjects *during* the Vm. Diodrast studies in one normal subject demonstrated blockade of inferior vena caval inflow during the Vm, whereas in a patient in congestive heart failure, diaphragmatic blockade of inferior vena caval inflow during the Vm was absent. The lack of a "venous blockade" is attributed by Judson and colleagues[3] to an elevated right ventricular end-diastolic pressure. In regard to this concept, studies during cardiac catheterization in 2 of our patients may be of interest. Each had compensated congenital heart disease with an interatrial septal defect and a minor degree of pulmonic or infundibular stenosis. One, with a markedly abnormal phase II pulse pressure (ratio A +28 per cent), had virtually identical inferior vena caval and right atrial pressures during a Vm, suggesting little or no venous blockade; nevertheless the resting right ventricular end-diastolic pressure was only 5 mm. Hg. A gradient of 2 mm. Hg from the inferior vena cava to the right atrium during a Vm was demonstrated in the second patient by simultaneously recording the pressures with a double-lumen catheter; her ratio A was only −8 per cent, and her resting right ventricular end-diastolic pressure varied from 5 to 7 mm. Hg.

When Judson and associates suddenly decreased the effective blood volume in patients in congestive heart failure by application of venous congesting cuffs on the thighs, or by venesection, their "failure response" became more nearly normal. Occurrence of a failure response in their normal subjects following an acute increase in circulating blood volume implied that impairment of cardiac function is not the sole explanation of abnormal phase II responses. Consequently, it would be of interest to correlate measured total blood volume with Vm response; unfortunately the data are thus far not available.

When there is effective blockade of venous inflow into the thorax during the Vm, as in the normal, or the usual compensated cardiac patient, the magnitude of phase II pulse pressure decline may be expected to vary inversely with the pulmonary blood volume. If so, this would be in accord with Sjöstrand's concept[10] of the pulmonary blood "reserve" or "depot" serving as a regulator of the circulation.

Studies by Rushmer[11] in normal subjects suggest that venous flow from the abdomen to the thorax may persist during the Vm if leakage of air occurs during the strain, or if it is not preceded by a deep inspiration. Either failure to obtain the prerequisite full inspiration preceding the Vm, or an undetected leakage of air during the maneuver may partially explain the abnormal phase II pulse pressure response found in several of our compensated patients.

Normal phase II responses (ratio A) were frequently noted despite either cardiac enlargement, severe stenosis or insufficiency of mitral or aortic valves, or a history of cardiac decompensation, *provided* no physical signs of heart failure were evident at the time of the Vm. These observations are in accord with those of Judson and associates.[3] But phase II response fails to discriminate between class I, II, and III cardiacs (New York Heart Association) or between normal and markedly subnormal exercise tolerance (PFI), if manifestations of decompensation are absent.

Thus abnormal phase II, providing certain technical prerequisites are adhered to (preceding full inspiration, nonleakage of air during the strain), may reflect right ventricular failure.

The relative importance of physiologic acute and chronic alterations in the blood volume modifying phase II of the Vm remains to be elucidated. In a general sense, the degree of "venous blockade" attained during the Vm, and thereby the magnitude of phase II pulse pressure response, depends on the pressure gradient between increased intrathoracic air pressure during Vm and the pressure-volume relationships of the right heart and systemic veins entering the thoracic cavity. Consequently both false positive and false negative abnormal phase II responses to Vm may be observed in relation to heart disease.

Summary and Conclusions

Arterial blood pressure was directly recorded during the Valsalva maneuver (Vm) in 44 cardiac patients and 19 control subjects.

Patients with definite physical signs of cardiac decompensation may exhibit an abnormal response in phase II, but not necessarily.

Abnormal phase II response may be observed despite cardiac compensation.

Abnormal phase II responses to the Valsalva maneuver in cardiac patients are more closely associated with physical signs of congestive heart failure than either impaired functional capacity or exercise tolerance, but both false positive and false negative responses may be observed.

Summario in Interlingua

Le pression de sanguine arterial esseva registrate directemente durante le experimento de Valsalva in 44 patientes cardiac e 19 subjectos de controlo.

Patientes con definite signos physic de discompensation cardiac pote, sed non debe, exhibir un responsa anormal in phase II.

Anormal responsas in phase II pote esser observate in despecto de compensation cardiac.

Anormal responsas in phase II es associate plus nettement con signos physic de congestive disfallimento cardiac que con reducite capacitate functional o tolerantia a exercitios, sed i occurre responsas pseudopositive e pseudo negative.

References

[1] Dawson, P. M.: An historical sketch of the Valsalva experiment. Bull. Hist. Med. **14:** 295, 1943.

[2] Elisberg, E., Singian, E., Miller, G., and Katz, L. N.: The effect of the Valsalva maneuver on the circulation. III. The influence of heart disease on the expected poststraining overshoot. Circulation **7:** 880, 1953.

[3] Judson, W. E., Hatcher, J. D., and Wilkins, R. W.: Blood pressure response to the Valsalva maneuver in cardiac patients with and without congestive failure. Circulation **11:** 889, 1955.

[4] Sharpey-Schafer, E. P.: Rapid methods of assessing heart failure. Scientific Session, Oregon Heart Association Meeting, October 1, 1954.

[5] Hamilton, W. F., Woodbury, R. A., and Harper, H. T., Jr.: Physiological relationships between intra-thoracic, intra-spinal and arterial pressures. J. A. M. A. **107:** 853, 1936.

[6] Bruce, R. A., Lovejoy, F. W., Jr., Yu, P. N. G., and McDowell, M. E.: Evaluation and significance of physical fitness for moderate work. Arch. Ind. Hyg. & Occ. Med. **4:** 236, 1951.

[7] Sarnoff, S. J., Hardenbergh, E., and Whittenberger, J. L.: Mechanism of the arterial pressure response to the Valsalva test. Am. J. Physiol. **154:** 316, 1948.

[8] Candel, S., and Ehrlich, D. E.: Venous blood flow during the Valsalva experiment including some clinical applications. Am. J. Med. **15:** 307, 1953.

[9] Stucki, P., Hatcher, J. D., Judson, W. E., and Wilkins, R. W.: Studies of circulation time during the Valsalva test in normal subjects and in patients with congestive heart failure. Circulation **11:** 900, 1955.

[10] Sjöstrand, T.: The significance of the pulmonary blood volume in the regulation of the blood circulation under normal and pathological conditions. Acta med. scandinav. **145:** 155, 1953.

[11] Rushmer, R. F.: Circulatory effects of three modifications of the Valsalva experiment. Am. Heart J. **34:** 399, 1947.

The Effect of Beta Sitosterol on the Serum Lipids of Young Men with Arteriosclerotic Heart Disease

By JOHN W. FARQUHAR, M.D., RALPH E. SMITH, M.D., AND MARY E. DEMPSEY, M.S.

Previous studies in human beings on unrestricted diets have indicated that the plant sterols (beta or gamma sitosterol) cause decreases in serum cholesterol. In this study, 15 young men with previous myocardial infarction were given 12 to 18 Gm./day of beta sitosterol with resultant sustained reductions of serum cholesterol and beta lipoprotein lipid. Lipoprotein lipid fractionation was performed by paper electrophoresis. These changes occurred irrespective of initial serum cholesterol or content of diet. Control observations of the effects of diet, weight maintenance, and the inclusion of placebos brought about increased confidence that the changes were due to the administered sitosterol.

THE search for agents capable of modifying the serum lipids of man was stimulated by the observation of Peterson in 1951[1] that the usual hypercholesterolemia of chicks fed cholesterol-enriched diets was prevented by the addition of plant sterols to the diet. In a similar study, Pollak[2] described the same phenomenon in rabbits. Hernandez and Chaikoff[3] found that the recovery of C^{14} labeled cholesterol from the thoracic duct of cholesterol-fed rats was substantially reduced by the addition of as little as 4 mg. of sitosterols to a meal containing 100 mg. of cholesterol. Subsequent investigators have reported decreases in serum cholesterol in normal and hypercholesterolemic human beings given varying doses of the plant sterols, gamma and beta sitosterols.[4-6]

More recently, Best and co-workers[7] reported decreases in serum phospholipid, cholesterol, total lipid, and S_f3-100 lipoproteins after beta sitosterol administration. The reductions in phospholipid and lipoproteins were less consistent and less marked than the changes in serum cholesterol and total lipid. The only negative report to date is that of Wilkinson and co-workers[8] who recently found that sitosterol was ineffective in lowering the serum cholesterol of man. Their observations were limited to 4 patients, 3 of whom had initial serum cholesterols of 200 mg./100 ml. or less. No placebo periods were included in their study.

This study was undertaken to evaluate the effects of β-sitosterol on the serum lipids in patients with arteriosclerotic heart disease, with careful attention to the control of diet, weight, and activity variables.

METHODS AND MATERIALS

Fifteen normotensive, nondiabetic men between the ages of 26 and 45, who had sustained previous well documented myocardial infarction, were studied with serial serum lipid determinations during a 3-phase study: (1) a premedication period of 6 to 12 weeks, (2) a period of sitosterol administration of 12 to 24 weeks, (3) a period of placebo administration of 10 to 16 weeks.

The placebo preparation was similar in taste and appearance to the sitosterol and none of the patients were aware of the change.

Prior to the first phase of the study all patients were placed on diets designed to maintain constant weight. The per cent of calories from fat was from 23 to 28 per cent in 9 patients and from 40 to 48 per cent in 6 patients. With the exception of 1 patient who lost 8 pounds during the first phase, the weights of all the patients were maintained to within 3 pounds of their initial values.

Cholesterol intake was from 200 to 300 mg./day in the 9 patients on fat-restricted diets and 900 to 1000 mg./day in the 6 patients on diets "normal" in fat content. The original diets, and all revisions necessary to maintain constant weight, were made up by a member of the dietetic staff. No effort was made to measure the percentage of fat from animal

From the Cardiovascular Disease Laboratory, Veterans Administration Hospital and University of Minnesota, Minneapolis, Minn.

Presented in part at Western Section of American Federation for Clinical Research, Carmel, California, Jan. 26, 1956.

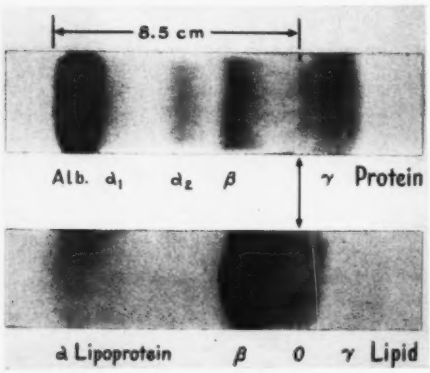


FIG. 1. Paper strips after electrophoretic separation and staining. Upper strip stained for protein (bromphenol blue) with albumin and globulin fractions labeled. Lower strip stained for lipid with Sudan black-B. The α-lipoprotein lipid fraction appears in the region of albumin-α-1 globulin; the β-lipoprotein lipid in the region of β-globulin; the origin lipid at the point of application; and the γ-lipid within a 2 cm. area on the cathode side of the center of the strip. Serum was applied evenly across the width of the strip, using 0.015 ml. for protein and 0.04 ml. for lipid.

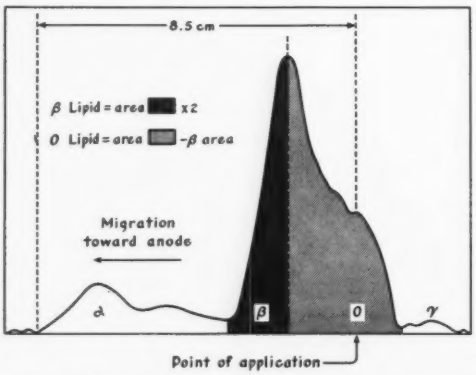


FIG. 2. Tracing of the lipid strip after densitometry showing planimetric method of separation of β-lipoprotein lipid from origin lipid. The peak of the β area is bisected and the area multiplied by 2 to obtain total β-lipoprotein area. This "β" area is then subtracted from the total area to obtain origin lipid area. The mg./100 ml. of stainable lipid is then computed by comparison with the total lipid value of the serum.

or vegetable sources, but the proportions of these types of fat did not vary much since all patients followed their prescribed diets.

Three equal portions of β-sitosterol* were given orally immediately before meals in total amounts of 12 to 18 Gm./day. During all phases of the study the patients were ambulatory, and efforts were made to achieve a "steady state" in respect to exercise, diet, and body weight.

Fifteen apparently normal men matched for age with the 15 study patients had serum lipid measurements for comparative baseline studies.

Serum was obtained in the fasting state at weekly or biweekly intervals during all phases. Serum was analyzed for cholesterol by the method of Abell,[9] total lipid by the method of Swahn,[10] and lipoprotein lipid calculated by protein and lipid staining of paper strips separated by electrophoresis. The electrophoresis was performed in an apparatus similar to that described by Durrum and associates,[11] using 6 35 cm. by 2.5 cm. Whatman 3 MM.† strips run for 12 hours at 6 C. in barbital buffer of pH 8.6 and ionic strength 0.05. Alternate strips were stained for protein with bromphenol blue and for lipid with Sudan black-B (fig. 1). The various lipid fractions of the stained strips were assigned proportional values by densitometric and planimetric measurement. The mg./100 ml. of stainable lipid was computed by comparison with the total lipid value of each serum sample. A technic was devised that we believed allowed more precise measurement of β-lipoprotein lipid by effecting its separation from the predominantly neutral fat "origin" lipids (fig. 2). Refine-

TABLE 1.—*Comparison of Normal Control and Abnormal Patient Groups*

No. of Patients (all males)	Normal (15) Mean ± σ*	Abnormal† (15) Mean ± σ	p‡
Age	35	36	
Weight (lb.)	170	166	
Total protein Gm./100 ml.	6.6 ± 0.4	7.0 ± 0.3	<0.01
Cholesterol mg./100 ml.	213 ± 34	291 ± 50	<0.001
Total lipid mg./100 ml.	965 ± 160	1204 ± 146	<0.001
α Lipid mg./100 ml.	262 ± 65	224 ± 43	<0.1
β Lipid mg./100 ml.	419 ± 96	557 ± 98	<0.001
Origin lipid mg./100 ml.	248 ± 95	387 ± 90	<0.001
γ Lipid mg./100 ml.	36 ± 18	36 ± 15	>0.9
β + Origin lipid mg./100 ml.	667 ± 155	944 ± 140	<0.001

* Standard deviation, $\sigma = \sqrt{\frac{\Sigma(x - \bar{x})^2}{N - 1}}$

† Measurements represent combined Means of premedication and placebo periods.

‡ Probability that the differences between Means are due to chance alone.

* Supplied by Eli Lilly and Company, Indianapolis, Ind.

† "Chromatography Grade."

TABLE 2.—*Mean Serum Cholesterol Changes in Patients with Arteriosclerotic Heart Disease During Beta Sitosterol Therapy*

Period	Cholesterol mg./100 ml. Mean ± σ	p Value	Mean Diff. mg./100 ml.*	Mean % Change
Premedication	293 ± 48			
		<0.001	51	17 (drop)
Sitosterol	242 ± 39			
		<0.001	46	16 (rise)
Placebo	288 ± 55			

* Standard error of difference

$$SE_{M_1-M_2} = \sqrt{\sigma^2_{M_1} + \sigma^2_{M_2}}$$

ments including low temperature control allowed satisfactory reproducibility of results.*

RESULTS

Comparison of the 15 study patients with 15 "normals" matched for age revealed significantly lower mean values in the normal group for β-lipoprotein and origin lipids, for total serum lipid, for protein, and for cholesterol (table 1).

A prompt fall in serum cholesterol occurred during the first 2 to 3 weeks of sitosterol. No tendency to return to pretreatment values was noted when sitosterol was taken for as long as 6 months. A similar prompt rise in serum cholesterol was noted within 3 weeks following substitution of placebo for sitosterol, the mean level of 288 mg./100 ml. during this phase being only 6 mg./100 ml. below the premedication mean of 293 mg./100 ml. The mean serum cholesterol values of the subjects during each phase of the study are summarized in tables 2 and 3.

Figure 3 expresses the changes in serum cholesterol in a different manner; the per cent deviation of each value from the mean of each patient is plotted on the ordinate, and the weeks of each phase of the study are plotted on the abcissa.

A lowering of β-lipoprotein lipid proportional in magnitude to that of cholesterol was observed during the sitosterol period; in contrast, there was no change in origin or γ-lipids. A slight rise in α-lipoprotein lipid occurred during the sitosterol period, this change being statistically less significant than the change in β-lipoprotein lipid.

The 3 patients with control serum cholesterol levels below 250 mg./100 ml. had de-

* Duplicate determinations agreed to within: ±6.5 per cent for alpha, ±7.6 per cent for beta, ±8.7 per cent for origin, and ±3.7 per cent for total lipids.

TABLE 3.—*Effect of Beta sitosterol on Serum Cholesterol of Fifteen Patients with Arteriosclerotic Heart Disease*

Patient	Age	A* Premedication period Mean ± σ	B Sitosterol period Mean ± σ	C Placebo period Mean ± σ	Change† A to B mg./100 ml.	Change† A to B p	Change† B to C mg./100 ml.	Change† B to C p
1. L.D.	33	220 ± 2	187 ± 14	217 ± 4	−33	<0.01	+30	<0.01
2. L.B.	35	220 ± 13	187 ± 13	220 ± 13	−33	<0.01	+33	<0.01
3. R.T.	26	234 ± 16	186 ± 9	233 ± 15	−48	<0.001	+47	<0.001
4. L.S.	43	260 ± 21	246 ± 15	280 ± 16	−14	<0.5	+34	<0.01
5. D.L.	29	270 ± 21	224 ± 13	272 ± 11	−46	<0.01	+48	<0.001
6. J.A.	38	271 ± 6	198 ± 11	216 ± 9	−73	<0.001	+18	<0.02
7. J.E.	37	272 ± 6	243 ± 10	286 ± 33	−29	<0.01	+43	<0.01
8. W.R.	42	284 ± 4	265 ± 13	318 ± 17	−19	<0.02	+53	<0.001
9. M.M.	33	307 ± 10	240 ± 8	302 ± 7	−67	<0.001	+62	<0.001
10. W.Li.	33	307 ± 7	264 ± 18	298 ± 13	−43	<0.01	+34	<0.01
11. J.L.	37	322 ± 21	270 ± 9	324 ± 20	−52	<0.01	+54	<0.001
12. A.S.	45	344 ± 0	210 ± 7	252 ± 12	−134	<0.001	+42	<0.001
13. J.P.	43	353 ± 12	246 ± 6	353 ± 12	−107	<0.001	+107	<0.001
14. W.L.	40	366 ± 12	356 ± 12	384 ± 17	−10	<0.3	+28	<0.02
15. R.L.	29	367 ± 38	320 ± 20	365 ± 25	−47	<0.02	+45	<0.02

* Mean number of determinations per patient: period A, 4.8; period B, 10.1; period C, 8.2.
† See note table 2.

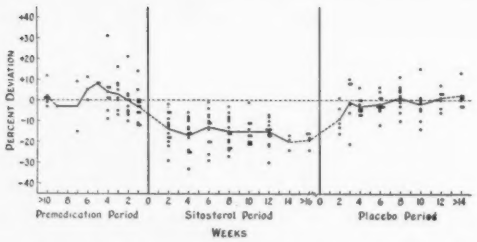


FIG. 3. Serum cholesterol changes during the sitosterol and placebo periods. Each patient's cholesterol values are plotted as per cent deviation from their own control Mean cholesterol. Each dot represents 1 cholesterol value (for patients on a biweekly schedule) or the Mean of 2 cholesterol values (for patients on a weekly schedule). This graph best portrays the prompt and sustained cholesterol reduction occurring after sitosterol administration and the prompt rise on substitution of placebo.

TABLE 4.—*Summary of Mean Changes in Total Lipid and Lipoprotein Lipid Fractions*

Lipoprotein lipid	Control period* mg./100 ml. Mean ± S.D. X^1	Sitosterol period mg./100 ml. Mean ± S.D. X^2	Difference mg./100 ml. $X^2 - X^1$	
α	224 ± 43	258 ± 46	+34	<0.02
β	557 ± 98	458 ± 113	−99	<0.001
Origin	387 ± 90	393 ± 79	+6	<0.8
γ	36 ± 15	38 ± 16	+2	<0.8
β + Origin	944 ± 140	850 ± 157	−94	<0.001
Total Lipid	1204 ± 146	1146 ± 152	−58	<0.001

* Premedication and placebo periods are combined as "control period."

creases of similar magnitude to those with control cholesterol levels above 250 mg./100 ml.

No significant difference in response was noted in the 2 dietary groups.

A slight but statistically significant drop occurred in total lipid during the period of sitosterol administration. Table 4 summarizes the mean changes in total lipids and lipoprotein lipid fractions. All values are included save for the 2-week period immediately following substitution of the placebo for sitosterol. In tables 4 and 5 the premedication and placebo periods are combined as the "control" period.

No untoward effects of sitosterol were observed during the period of observation; the preparation was palatable and well tolerated by all patients.

TABLE 5.—*Summary of Individual Changes in Total Lipid and Lipoprotein Lipid Fractions after Beta Sitosterol Administration*

Values in mg./100 ml. of stainable lipid.

Patient	Total lipid mg./100 ml.		α-lipoprotein lipid mg./100 ml.		β-lipoprotein lipid mg./100 ml.		Origin lipid mg./100 ml.		γ-lipid mg./100 ml.	
	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol
1. L.D.	1034	1048	165	259	448	345	374	406	47	38
2. L.B.	1081	1053	280	202	400	391	363	444	38	16
3. R.T.	1021	900	248	299	578	326	173	235	22	40
4. L.S.	1342	1337	289	296	532	511	486	504	35	26
5. D.L.	1149	1166	176	268	528	497	416	330	29	71
6. J.A.	1008	894	212	240	454	335	310	293	32	26
7. J.E.	1340	1305	251	231	562	595	504	455	23	24
8. W.R.	1170	1140	236	301	551	426	340	366	43	47
9. M.M.	1289	1103	282	343	580	414	354	329	73	17
10. W.Li.	1148	1094	176	188	504	465	442	395	26	46
11. J.L.	1367	1290	194	208	602	532	518	498	53	52
12. A.S.	1169	1109	181	292	628	310	337	481	23	26
13. W.L.	1487	1402	243	279	802	669	427	395	15	59
14. R.L.	1247	1215	203	208	625	594	375	366	44	47
Mean	1204	1146	224	258	557	458	387	393	36	38
σ	146	152	43	46	98	113	90	79	15	16
p	<0.001		<0.02		<0.001		<0.8		<0.8	

DISCUSSION

The known variability of serum cholesterol and β-lipoprotein[12] makes it advisable to include a number of measurements of these values. Use of placebos and control of diet and body weight add further confidence that observed changes are due to the medication given. Under these circumstances β-sitosterol effects prompt and sustained reductions of serum cholesterol, total lipid, and β-lipoprotein lipid of a moderate degree, with small increases occurring in α-lipoprotein lipid. These changes occur in patients with serum cholesterols not in the range usually considered as hypercholesterolemic and occur despite previous moderate fat and cholesterol limitation.

It has been adequately proved that sitosterols lower the serum cholesterol of man,[5-7] and prevent increases in liver and plasma cholesterol of laboratory animals fed diets high in cholesterol.[1, 2, 13-15] However, the mechanisms of these actions are unknown.

An attractive postulate is that sitosterol competes with cholesterol for available fatty acids, bile salts, and the enzyme used in cholesterol esterification, thereby interfering with cholesterol absorption.[7, 14] Swell and co-workers[14] have shown that soy sterols are esterified in vitro in the presence of pancreatic cholesterol esterase, the rate of esterification being only slightly less than that of cholesterol. In contrast to the action of free sitosterol, Best, Duncan, and Wathen[16] have found that sitosterol esters do not prevent increases in tissue lipids in myxedematous rats. This latter finding furnishes indirect support for the hypothesis that sitosterol acts by interfering with esterification of cholesterol.

A second postulate of the action of sitosterol is that it combines with cholesterol in the gut to form a more stable, less absorbable complex.[2] This union may be similar to that complex formed in the Liebermann-Burchard reaction between cholesterol and digitonin, another sterol.

Either postulate assumes inhibition of absorption of both dietary cholesterol and that portion of endogenous cholesterol excreted in the bile. Since both dietary and biliary cholesterol are predominantly in the free form, there is no reason to believe sitosterol would differentiate between them.

Although studies to date would indicate that sitosterol acts on cholesterol absorption, further work is needed to determine its relationship to the transport, metabolism, and excretion of cholesterol and lipoproteins.

The possible role of sitosterol in the treatment of human atherosclerosis has not been established, nonetheless the lack of known side effects and the observed modification of serum lipids would indicate potential benefit from its use.

Summary

Baseline serum lipid values of 15 normotensive nondiabetic young men with arteriosclerotic heart disease are reported and compared with an apparently normal group matched for age. The abnormal group was characterized by significantly increased cholesterol, beta lipoprotein lipid, and total lipid.

In this abnormal group, β-sitosterol administration resulted in highly significant reductions in serum cholesterol and β-lipoprotein lipid, with a lesser reduction in total lipid and a slight rise in α-lipoprotein lipid.

The apparent lack of deleterious effects, coupled with the observed changes, suggests potential benefits of sitosterol administration. Its role as a therapeutic agent in clinical medicine has not yet been established.

Summario in Interlingua

Es reportate valores de base pro lipido seral, observate in 15 normotensive e non-diabetic juvene adultos mascule con morbo cardiac arteriosclerotic. Le valores es comparate con illos obtenite ab un secunde e apparentemente normal gruppo de individuos de etates correspondente. Le gruppo anormal esseva characterisate per augmentos significative de cholesterol, lipido beta-lipoproteinic, e lipido total.

In iste gruppo anormal, le administration de beta-sitosterol resultava in significativissime reductiones del cholesterol seral e del lipido beta-lipoproteinic, accompaniate de minus marcate reductiones de lipido total e un leve augmento del lipido alpha-lipoproteinic.

Le apparente absentia de effectos nocive, insimul con le supra-mentionate alterationes, indica possibilemente que le administration de sitosterol resulta in effectos benefic. Le rolo de sitosterol como agente therapeutic in le medicine clinic es non ancora establite.

Acknowledgment

The authors wish to express their appreciation to Miss Ardelle Mead and Mr. Thomas Jenny for technical assistance, and to Mrs. Janet Wesselman for preparing the diets.

REFERENCES

[1] Peterson, D. W.: Effect of soybean sterols in the diet on plasma and liver cholesterol in chicks. Proc. Soc. Exper. Biol. & Med. **78:** 143, 1951.

[2] Pollak, O. J.: Successful prevention of experimental hypercholesterolemia and cholesterol atherosclerosis in the rabbit. Circulation **7:** 696, 1953.

[3] Hernandez, H. H., and Chaikoff, I. L.: Do soy sterols interfere with absorption of cholesterol? Proc. Soc. Exper. Biol. & Med. **87:** 541, 1954.

[4] Pollak, O. J.: Reduction of blood cholesterol in man. Circulation **7:** 702, 1953.

[5] Best, M. M., Duncan, C. H., Van Loon, E. J., and Wathen, J. D.: Lowering of serum cholesterol by the administration of a plant sterol. Circulation **10:** 201, 1954.

[6] Barber, J. M., and Grant, A. P.: The serum cholesterol and other lipids after administration of sitosterol. Brit. Heart J. **17:** 296, 1955.

[7] Best, M. M., Duncan, C. H., Van Loon, E. J., and Wathen, J. D.: The effects of sitosterol on serum lipids. Am. J. Med. **19:** 61, 1955.

[8] Wilkinson, C. F., Boyle, E., Jackson, R. S., and Benjamin, M. R.: Effect of varying the intake of dietary fat and the ingestion of sitosterol on lipid and lipoprotein fractions of human serum. Metabolism **4:** 302, 1955.

[9] Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem. **195:** 357, 1952.

[10] Swahn, B.: Studies on blood lipids. Scandinav. J. Clin. & Lab. Invest., Suppl. 8, **5:** 1953.

[11] Williams, F. G., Jr., Pickels, E. G., Durrum, E. L.: Improved hanging-strip paper-electrophoresis. Science **121:** 829, 1955.

[12] Watkin, D. M., Lawry, E. Y., Mann, G. V., and Halperin, M.: A study of serum beta lipoprotein and total cholesterol variability and its relation to age and serum levels in adult human subjects. J. Clin Invest. **33:** 874, 1954.

[13] Peterson, D. W., Shneour, E. A., and Peek, N. F.: Effects of dietary sterols and sterol esters on plasma and liver cholesterol in the chick. J. Nutrition **53:** 451, 1954.

[14] Swell, L., Boiter, T. A., Field, H., and Treadwell, C. R.: Esterification of soybean sterols in vitro and their influence on blood cholesterol level. Proc. Soc. Exper. Biol. & Med. **86:** 295, 1954.

[15] Burke, K. A., McCandless, R. F. J., and Kritchevsky, D.: Effect of soybean sterols on liver deposition of cholesterol-C^{14}. Proc. Soc. Exper. Biol. & Med. **87:** 87, 1954.

[16] Best, M. M., Duncan, C. H., and Wathen, J. D.: Effect of sitosterol on the hyperlipemia of myxedema. Abstracted, Circulation **12:** 482, 1955.

Enos, W. F., Jr., Beyer, J. C., and Holmes, R. H.: Pathogenesis of Coronary Disease in American Soldiers Killed in Korea. J. A. M. A. **158:** 912 (July 16), 1955.

The authors have previously reported a series of 300 American soldiers killed in Korea, in 77.3 per cent of whom, some gross evidence of coronary disease was demonstrated. The present paper discusses all available clinical data and reviews the histopathology of the lesions. Complete records were available on 200 men. The average age was noted to be 22.1 years, average height 5 ft. 7¾ in. and average weight 145.8 lb. The gross and microscopic studies indicate that the coronary lesions are due in part to intravascular stress caused by the hemodynamics of the coronary circulation, as modified by anatomic factors. The stress results in subendothelial fibroblastic proliferation, deposition of a mucoid ground substance, and fragmentation of the internal elastic membrane. It is of interest to compare the lesions found in the American soldiers with the lesions found in a small series of Japanese natives now being studied. Thirty Japanese men, approximating the age group of the American soliders, were found in material from 114 cases studied in Japan. The amount and distribution of the lipids on the elastica and within the parenchyma of the plaques found in the Americans, as compared to the Japanese, indicate that certain plasma lipids, as modified by diet, are another important agent in the development of coronary disease in young males.

Kitchell

Comparison of Limb and Precordial Vectorcardiographic Systems

By Ernest Frank, Ph.D., and George E. Seiden, M.D.

Two advanced types of vectorcardiographic systems have been applied to 104 miscellaneous patients for the purpose of comparing practical features and electric results. The 2 systems showed satisfactory average agreement, as expected, but there were marked individual differences in many cases. Despite corrections for torso shape and typical eccentric ventricle location, the limb electrode system yielded results significantly outside attainable limits, and hence is considered unsatisfactory for quantitative work despite its practical advantages.

A RECENTLY described system of vectorcardiography[1] that is practical for clinical use employs 7 electrodes (3 on the precordium) and has the advantages of (1) sound theoretic and physical basis, (2) corrections for shape of human torso, (3) exclusion of left arm electrode with its attendant errors, (4) insensitiveness to individual variability of dipole location, (5) reasonable speed and ease of application, (6) better signal-to-noise ratio than in "remote electrode" systems, and (7) cost comparable to other systems. Its disadvantages are criticalness of location of some electrodes and need for rubbing the skin beneath electrodes (which can be avoided by use of cathode followers). An "average computing" system[2] employing 4 electrodes (the minimum possible number) on highly practical body sites (R, L, F, B) incorporates corrections for torso shape, largely overcomes the disadvantage of critical electrode placement, and employs fewer electrodes. Therefore, it is easier and faster to apply, although the need for skin rubbing is still present. However, it has the disadvantages of errors traceable to individual dipole location variability among subjects and to individual variability of left arm electric characteristics. Also it produces only one half the signal amplitude of the precordial system and thus is more susceptible to muscle-tremor artifacts.

The practical advantages for clinical use of the average computing system suggest a comparative study to ascertain directly, in terms of vector loops on the same patient, the degree of correspondence between results of the 2 systems. The essential purpose of the study was to discover if the more accurate but more elaborate precordial system yields significantly different quantitative results in a sufficient number of cases to justify its use. The 2 systems were not expected to give the same results in all cases. A study[3] of cardiac patients indicated significant differences in individual dipole location, and model studies[2] indicated that dipole location effects introduce sizable error in the average computing system. Moreover, left arm variability was also anticipated as a source of error. Despite these negative theoretic indications, practical advantages of the average computing system were felt to be too attractive to discard without direct experimental evidence. Moreover, a comparative study of this type gives additional evidence (though less sharply than in other studies[4, 5]) concerning applicability of dipole potentials in 3-dimensional torso models to a wide assortment of patients.

Method and Material

Because choice of subjects can influence comparison of the 2 systems, a wide variety of patients, both male and female, with and without heart disease, and of varied age and body build, were chosen for study. Of the 104 patients selected, 69 were male and 35 were female. The age range was from 7 to 78 years (average 52). The range for height was 46 to 74 inches (average 68); for weight, 46 to 293 pounds (average 150). Clinical and standard V lead electrocardiographic diagnoses are given in table 1.

Five electrodes of the precordial system were

From the Moore School of Electrical Engineering, University of Pennsylvania and the Edward B. Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia, Pa.

This investigation was supported in part by U. S. Public Health grant H-339-C.

TABLE 1.—*Diagnoses of 104 Patients*

Clinical diagnosis	No.	ECG diagnosis	No.
No heart disease	40	Normal	40
Coronary artery disease	28	Nonspecific abnormality	21
Rheumatic heart disease	13	Left ventricular hypertrophy	20
Hypertensive heart disease	11	Borderline normal	8
Cor pulmonale	5	Right ventricular hypertrophy	6
Syphilitic heart disease	4	Anterior wall infarction	5
Miscellaneous	3	Posterior wall infarction	4

attached around the thorax at the left side, A; right side, I; front, E; back, M; and on the left precordium, C, in locations that have been accurately prescribed.[1] Electrode level was determined by an electrical technic previously described[1] for each of the 104 patients. The remaining 2 electrode sites were left leg, F, and back of the neck, H. These electrode potentials were delivered through cathode followers (to avoid the need of skin rubbing) to the network of resistors shown in figure 1 (left), any 2 outputs of which could be amplified in a 2-channel vectorcardiograph and displayed on a cathode-ray oscilloscope.

The 4 electrodes of the average computing system were attached to the standard limbs (right arm, R; left arm, L; left leg, F) and on the back, B, 1 inch to the left of the midline at the same level as in the precordial system. These electrode potentials were delivered through cathode followers to the network of resistors shown in figure 1 (right), any 2 outputs of which were fed into the same vectorcardiograph as in the precordial system. The resistance network serves essentially as an analogue computer that, in effect, solves 3 equations of the type published previously[2] that pertain to a typical dipole location designated as no. 22.[6] The average computing system must not be confused with the Wilson tetrahedron, despite use of the same electrode sites.

These 2 systems represent considerable contrast, especially regarding the transverse components, since one employs "remote" electrodes exclusively while the other has several electrodes in close anatomic proximity to the heart. Nevertheless, it was expected on the basis of model studies[2] and experiments on a variety of subjects[6, 7] to find good agreement between the 2 systems in cases where the subject's dipole location did not differ too much from location no. 22. However, the amplitude level of the precordial system is established by a minimum image vector of 136 units[1] (for the head-foot component), while that of the average computing system is established by a minimum image vector of 71 units (for the front-back component). Thus, the amplitude

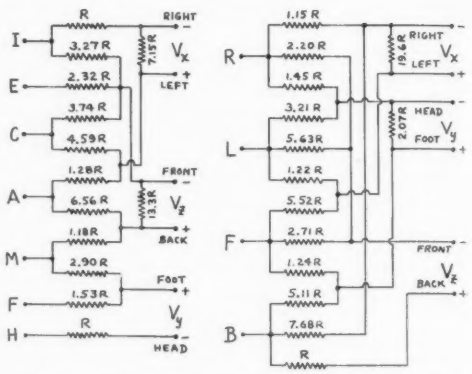


FIG. 1. Computing networks used in the limb (right) and precordial (left) systems. These networks serve to correct for torso shape and dipole location based upon results with internal dipole in homogeneous, 3-dimensional torso models. In addition, the precordial system electrodes and networks have been selected to yield results insensitive to location of the dipole. Shunt resistors across V_x and V_z in the precordial system and across V_x and V_y in the average computing system serve to equalize standardization factors. Networks have been designed with equal resistance levels to combat 60 cycle interference. The value of R was 50,000 Ω.

ratio expected was 71/136 = 0.52; that is, the size of the vector loops produced by the average computing system was expected to be 0.52 times that obtained in the precordial system when the subject's dipole location was no. 22. Accordingly, the standardization employed in the average computing system was routinely larger than in the precordial system by a factor of about 2 (1.8 was actually employed).

Subjects were studied in the sitting position except in cases where it was essential to employ the prone position because of excessive muscle-tremor interference in the low-signal average computing system. In each case frontal, sagittal, and transverse projections of the QRS loops of both systems were observed sequentially on the cathode-ray tube and photographed with a polaroid camera. In addition, scalar leads of the precordial system were displayed on the cathode-ray tube and photographed, and standard electrocardiograms of all subjects were obtained with a Visocardiette.

BASIS FOR COMPARISON OF LOOP PROJECTIONS

Comparison of projections of corresponding loops derived from the 2 systems is difficult to accomplish in quantitative terms. Since many of the QRS loops were qualitatively very similar, it was necessary to devise fairly exacting criteria for comparative purposes. A semiquan-

titative method was employed consisting of evaluation of 5 items covering pertinent characteristics of each projected loop (these items were not completely independent). Each item was given a score of either 2, 1, or 0 based on the criteria below, and a total evaluation score ranging from 10 to 0 was deduced for each pair of projected loops.

Direction of Inscription. Direction of inscription of the projected loop was indicated by intensity modulation of the cathode-ray tube. A score of 2 was assigned when direction of inscription was clearly the same in corresponding loops. A score of 1 was given in cases that were not absolutely clear in the records or when definite doubt existed as to agreement in cases that displayed multiple crossings. A score of 0 resulted in cases where direction of inscription was clearly opposite in corresponding loops.

Length-to-Width Ratio Comparison. A rough measure of over-all shape of projected loop can be formulated by defining a length-to-width ratio as follows: length of maximum vector (distance from null point to point of maximum displacement of loop) divided by maximum width of the loop measured along a line perpendicular to the maximum vector. Length-to-width ratio of each projected loop was determined with this definition. A score of 2 was given when the ratio of the larger to the smaller length-to-width ratio was in the range 1.0 to 1.4; a score of 1 was given when this ratio was between 1.4 and 2.0; a score of 0 was given for ratios exceeding 2.0.

Difference Between Angles of Maximum Vector. The angle of the maximum vector as seen in projection was measured with respect to the following reference axes: frontal, right-to-left reference axis (angle measured clockwise as observed from the front of the subject); sagittal, front-to-back reference axis (angle measured clockwise as observed from the left side of the subject); transverse, right-to-left reference axis (angle measured counterclockwise as observed from the head of the subject). Difference between angles obtained in the 2 systems was evaluated as follows: score 2 for differences between 0° and ±10°, score 1 for differences lying between ±11° and ±25°, score 0 for differences exceeding ±25°.

General Shape Agreement. General shape was defined as a quality dealing with the over-all appearance of the projected QRS loop with special attention paid to the Q and S deflections. A score of 2 was given if the over-all shape agreement was excellent and if Q and S deflections were in good quantitative agreement. A score of 1 was assigned in cases where over-all agreement was good but with some departures in relative sizes of the Q and S deflections. A score of 0 was given in cases with poor correspondence in over-all shape or when gross discrepancies in Q and S deflections existed, such as a sizable S wave in one loop and none in the other.

Fine Details of Shape. When fine details of loop contour such as slight quirks and peculiarities of contour were distinctly present and consistent in the pair of loops, a score of 2 was assigned. If most of the fine detail showed good correspondence except for 1 or 2 minor aspects, a score of 1 was given. A score of 0 resulted when there was no correspondence between fine detail in one loop as compared with the other.

Results

With 104 subjects a total of 312 loop projections was obtained. Results of the QRS loop comparison based on 5 items mentioned are shown in table 2. Numbers in this table represent the number of cases in each category but are nearly equal to per cent, since 104 cases are included in the study. On the whole, it may be seen from this table that agreement in frontal projections, F, was consistently better than in sagittal, S, and transverse, T, projections in all items except direction of inscription, while sagittal and transverse agreement is closely comparable. The 16 cases of score 1 in direction of inscription for frontal projections are largely

Table 2.—*Comparison of 312 QRS Loop Projections*

Score	Direction of inscription			Length-to-width ratio comparison			Difference between angles of maximum vector			General shape agreement			Fine details of shape		
	F	S	T	F	S	T	F	S	T	F	S	T	F	S	T
2	88	92	95	64	49	51	64	44	43	83	60	56	39	18	23
1	16	12	8	26	32	33	33	39	39	18	43	45	60	79	65
0	0	0	1	14	23	20	7	21	22	3	1	3	5	7	16

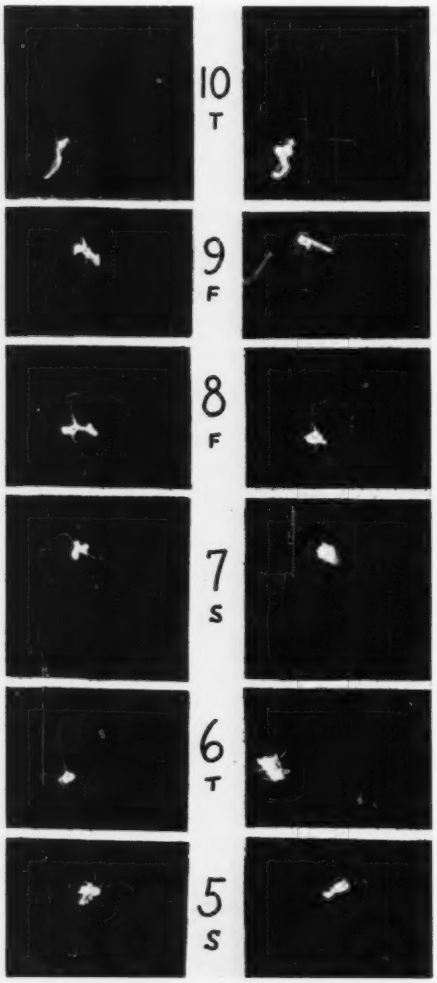


FIG. 2. Precordial system left, average computing system right. Sample records of projections of vector loops with accompanying comparison evaluation scores ranging from 10 through 5. F, S, T signify frontal, left sagittal, and transverse projections, respectively. Timing markers occur at a rate of 480/second, locked in at 8 times the line frequency. Bright spots immediately after blanked portions of trace reveal direction of inscription. Note additional muscle tremor in records on right, even though cleanest records were selected for this figure. Standardization employed in precordial loops was 1 inch/mv. and in average computing system 1.8 inch/mv. Faint lines have been drawn on records intersecting at the null point.

traceable to the fact that frontal loops were often nearly closed as compared with more open loops in the other views, with consequent ambiguity in direction of inscription in some cases.

Total evaluation scores for each pair of projected loops in 312 cases were distributed as follows: 16 received a score of 10, 60 a score of 9, 79 a score of 8, 74 a score of 7, 47 a score of 6, 15 a score of 5, 14 a score of 4, 6 a score of 3, and 1 a score of 2. Sample loops with corresponding over-all evaluation are shown in figure 2, and give a graphic idea of the exacting nature of the comparison criteria. However, it is not possible to give a representative record in each case, since there was an appreciable range of variation within each category. These over-all scores may be given descriptive designations as follows: score 10 excellent, 9 very good, 8 good, 7 fair, 6 fair-to-poor, 5 poor, 4 (or less) very poor. Scores based on purely subjective independent evaluation of the loops were usually within ± 1 point of those obtained from the more elaborate semiquantitative criteria.

Additional data on correspondence of results are presented in table 3. It may be seen that mean differences in angle of maximum QRS vector were only 2 or 3 degrees, which is essentially perfect average agreement. However, the standard deviation (σ) indicates that about two thirds of the cases were within $\pm 12°$ of the mean for the frontal loops, while the scatter in angle of the sagittal and transverse maximum vectors was approximately twice this amount. Amplitudes of corresponding QRS dipole components were, on the average, within ± 10 per cent of expectations based on model studies, as can be seen in table 3 on comparison

TABLE 3.—*Correspondence of QRS Results for 104 Patients*

	Difference in angle of maximum vector, degrees			Ratio of peak-to-peak amplitudes of corresponding dipole components			Comparison evaluation score		
	F	S	T	X	Y	Z	F	S	T
Mean	−2.1	3.5	−2.5	0.53	0.47	0.42	8.0	7.0	7.0
σ.....	12.1	23.8	20.2	0.15	0.09	0.15	1.4	1.6	1.6

with the theoretic amplitude ratio of 0.52, previously mentioned. The y-component had a significantly smaller standard deviation than the x- or z-components. The reason why the z-component average amplitude was disproportionately lowest of the 3 was that, in about one third of the cases, its amplitude was markedly smaller (0.3 or less) in the average computing system. Comparative evaluation scores in table 3 indicate that frontal loop agreement was significantly better and more tightly clustered than sagittal or transverse, but that sagittal and transverse comparison was substantially the same on the average.

Discussion

There were 2 major departures between results obtained with the 2 systems, the most pronounced of which was poor agreement, in many cases, in the front-back component, p_z. The most striking failure in correspondence of p_z was markedly reduced amplitude and altered timing, which was anticipated to occur in the average computing system when dipole location is about 2 cm. or more anterior to design-center location no. 22. In approximately one third of the cases, the p_z component was foreshortened by a relative factor of 2, or more, in comparison with the more accurate p_z of the precordial system, and its shape was also markedly different. An example of this type of result has been published previously.[1] A somewhat more pronounced example is shown in figure 2, score 5. The second important difference occurred in approximately 20 per cent of cases when the amplitude of the right-left component p_x in the average computing system substantially exceeded reasonable limits anticipated from model experiments. An illustration of this finding is given in figure 2, score 6. This may be traceable to electric peculiarities of the left arm of the subject.

Despite the above differences, similarities in the results also deserve emphasis. Agreement in shape, timing, and amplitude, of the head-foot component p_y was best of all 3 as expected, because the p_y lead in both systems is, as observed in models,[2] a very stable quantity. (As a practical matter, it should also be observed that the left leg electrode was involved in both systems as part of the p_y lead, which of course would tend to improve the correlation.) Although individual discrepancies were pronounced in many cases, *average* agreement between the 2 systems in terms of the measured quantities was within the ± 15 per cent error expected from applicability of model results to the human subject. This may be interpreted to mean that dipole location of subjects tested clustered around location no. 22. Good *average* agreement between these 2 distinctly different systems constitutes rough evidence of the applicability of dipole potentials in homogeneous 3-dimensional torso models to the human subject for a wide variety of normal and abnormal cases. However, the comparative study does not represent an exacting detailed test of model applicability.

Accuracy expected from the precordial system may be expressed roughly in terms of comparative evaluation scores. Scores between 8 and 10 cover the approximate range of absolute error expected in the precordial system. Therefore, it may be concluded that the frontal loops of the average computing system were, on the average, within the accuracy range of the precordial system but that both sagittal and transverse loops were, on the average, somewhat outside. In terms of individual cases, approximately 50 per cent of the 104 cases showed differences that were outside expected accuracy limits of the precordial system. The finding of best agreement in the frontal projection is consistent with that of a somewhat similar study of Burger and associates.[3] However, average frontal agreement in Burger's study ranged from 5.2 to 6.7 for various systems, rather than the 8.0 result obtained here. It is thought that this difference cannot be attributed to the subjective nature of the comparison basis, because very exacting criteria were used that would tend to lower our evaluation scores. The explanation would appear to reside in the fact that the precordial system, being less vulnerable to dipole location, provided a much more stable reference basis than in Burger's cases, where the systems compared were all susceptible to this critical parameter.

Although 3 projections of the spatial QRS loop have been used in this study, it should not be misconstrued that this is the most useful approach for interpretation of vector loops. Correlation of vector loops with heart activity for clinical purposes must entail a study of the loops in space, because loop *projections* can be influenced markedly by slight changes in orientation of the spatial loop. However, in a comparative study of this kind where it is only desired to compare 2 loops independently derived by 2 different systems, analysis of loop projections provides a more exacting basis of comparison than analysis of the spatial loop. Slight changes in loop orientation can cause extreme changes in some of the quantities used as a basis of comparison, the most glaring example of which is length-to-width ratio. It is likely that a more favorable comparison would have resulted if the 2 spatial loops had been compared, but the sizable discrepancies observed in p_x would still be present.

It should be emphasized that the average computing system is not equivalent to the Wilson tetrahedron despite use of the same electrode sites. The essential difference is that the average computing system corrects for human torso shape and for a typical eccentric dipole location, while the Wilson tetrahedron applies to a spherical boundary with a centric dipole. Since the latter representation is inferior to the former, correspondence of results between the Wilson tetrahedron and the precordial system may be expected to be much poorer than obtained here.

Many interesting characteristics of QRS loops found in this study include such quantities as absolute amplitude of components, angles of maximum vectors, directions of inscription, length-to-width ratios, and degree to which the spatial loop is confined to a plane. None of these data are considered worthy of reporting at this time because of the extreme heterogeneity of the group of subjects and insufficient number of cases of a given kind. Therefore, only relative and comparative data have been presented.

The essential conclusion reached after thorough analysis of results is that the precordial system is worth the additional effort for 3 reasons:

1. While agreement is quite satisfactory on the average, individual differences in 50 per cent of the cases were quantitatively significant.

2. Marked discrepancies in the front-back component in the average computing system (in one third of the cases) and significant differences in the right-left component (in one fifth of the cases) represent excessive individual departures giving results in some cases that are even qualitatively different.

3. As a purely practical matter, the muscle tremor interference in the average computing system was severe in many cases and gave difficulties that tended to offset its practical clinical advantages. This conclusion tacitly assumes that quantitative vectorcardiography will reveal information not heretofore found on a qualitative basis. The degree of inherent scatter of data for heart patients that is not presently known is, of course, a pertinent factor. It would seem advisable to use the best possible practical system until further basic data are obtained concerning inherent scatter. However, failure to obtain a consistently satisfactory p_x in the average computing system would seem to rule out this system in any event.

Summary

Results obtained with 2 advanced types of vectorcardiographic systems applied to an assorted group of 104 subjects are compared in quantitative terms. While average agreement between the 2 systems was satisfactory, individual differences in 50 per cent of cases were quantitatively significant. The most glaring defect of the limb electrode system was failure to render an accurate front-back dipole component in one third of the cases.

Acknowledgment

Technical assistance of Cynthia Hamilton and Deborah Packman is gratefully acknowledged.

Summario in Interlingua

Es comparate quantitativemente le resultatos obtenite in duo avantiate typos de systemas vectocardiographic, applicate a un assortimento

le 104 subjectos. Le accordo median del duo ;ystemas esseva satisfactori, sed in 50 pro cento lel casos le differentias individual esseva quan-itativemente significative. Le plus serie defecto lel systema a electrodos extremitatal esseva le acto que illo non provideva un accurate com-ponente dipolic fronto-dorsal in un tertio del asos.

REFERENCES

1 FRANK, E.: An accurate clinically practical system for spatial vectorcardiography. Circulation **13:** 737, 1956.

2 —: Analysis of R, L, F, B systems of spatial vectorcardiography. Am. Heart J. **51:** 34, 1956.

3 SEIDEN, G. E.: Anatomic location of the electric heart center in patients. Abstracted, Circulation **12:** 773, 1955.

4 FRANK, E.: Absolute quantitative comparison of instantaneous QRS equipotentials on a normal subject with dipole potentials on a homogeneous torso model. Circulation Research **3:** 243, 1955.

5 —, KAY, C. F., SEIDEN, G. E., AND KEISMAN, R. A.: A new quantitative basis for electrocardiographic theory: The normal QRS complex. Circulation **12:** 406, 1955.

6 —: Determination of the electrical center of ventricular depolarization in the human heart. Am. Heart J. **49:** 670, 1955.

7 SEIDEN, G. E., AND KEISMAN, R. A.: The precordial electrocardiogram: Is it derived predominantly from the heart muscle immediately beneath the electrode? Abstracted, J. Clin. Invest. **34:** 962, 1955.

8 BURGER, H. C., VAN MILAAN, J. B., AND DEN BOER, W.: Comparison of different systems of vectorcardiography. Brit. Heart J. **14:** 401, 1952.

Mann, G. V., Teel, K., Hayes, O., McNally, A., and Bruno, D.: Exercise in the Disposition of Dietary Calories. Regulation of Serum Lipoprotein and Cholesterol Levels in Human Subjects. New England J. Med. **253:** 349 (Sept. 1), 1955.

Four men, aged 24 years, were studied during a control period and during a 4-week period in which the caloric intake was doubled but the fat intake was kept constant at the control level. During this time the subjects were required to maintain their body weights within 5 pounds of the mean control weight by strenuous exercise. They were also studied during a third period of similar high caloric intake but without high energy expenditure, and finally, they were studied during a period of restricted caloric intake to remove the fat deposited during the third period. One of the 4 subjects left the experiment because of inability to maintain a constant weight during the period of high intake and high energy expenditure. The observations indicated that the subjects were able to double their caloric supply without increasing the level of their serum lipids so long as the excess energy was dissipated as exercise. When the excess energy was no longer dissipated as exercise, it was diverted to adipose tissue in 2 of the 3 subjects with an increase of serum cholesterol, phospholipid, and lipoprotein levels.

The experiment is felt to simulate in miniature the nutritional progress of an American male adult from early adulthood with high energy turnover associated with athletic endeavors, through a long period of diminishing activity but with unchanged dietary habits. The authors state that this leads in a variable time to an obese person at middle age, with poor muscular development and with elevated serum cholesterol and β-lipoprotein levels although without visible lipemia. The authors propose that the positive caloric balance over a long period elevates the serum lipid levels and contributes to atherogenesis.

ROSENBAUM

Coronary Blood Flow, Myocardial Oxygen Consumption, and Myocardial Metabolism in Normal and Hyperthyroid Human Subjects

By Leonard Leight, M.D., Valentino DeFazio, M.D., Frederick N. Talmers, M.D., Timothy J. Regan, M.D., and Harper K. Hellems, M.D.

The effects of thyroid hormone excess on myocardial hemodynamics and carbohydrate metabolism were determined in a group of subjects, and the findings compared with those obtained in a group of normal individuals. The results indicate that in thyrotoxicosis there tends to be an increase in coronary blood flow and myocardial oxygen consumption and a normal per cent extraction of oxygen by the myocardium. The metabolism of glucose, lactic acid, and pyruvic acid was virtually identical in the 2 groups. No relationship was demonstrable between the arterial levels of the carbohydrate substances and their extraction by the heart.

THE pronounced clinical effects of hyperthyroidism upon the cardiovascular system strongly suggest a direct participation of cardiac tissue in the metabolic effects of excess thyroid hormone. Although limited study of the human heart has failed to support this view,[1] experimental hyperthyroidism has revealed an increased myocardial oxidative activity[2, 3] and diminished myocardial concentration of high-energy phosphate compounds.[4]

This limitation in the source of immediately available energy for muscular contraction, and, hence, of cardiac work capacity, might represent a biochemical lesion responsible for the clinical demonstration of impaired exercise response in hyperthyroid patients.[5]

To explore further the influence of thyroid hormone excess on the myocardium, a study of carbohydrate metabolism, oxygen consumption, and coronary flow was undertaken in a group of individuals with typical hyperthyroidism and, for comparative purposes, in a group of hospitalized individuals free of cardiac and metabolic disease.

From the Cardiovascular Research Laboratory, Department of Medicine, Wayne University College of Medicine, and City of Detroit Receiving Hospital, Detroit, Mich.

This investigation was supported by research grants H-1492 from the National Heart Institute, U. S. Public Health Service, and a grant from the Michigan Heart Association.

Methods and Material

The data presented were obtained from 17 normal individuals and 13 hyperthyroid patients. The former group was made up of individuals convalescent from a variety of acute diseases, and at the time of study had no detectable cardiovascular or metabolic disease. The latter group was made up of patients with history, physical, and laboratory findings typical of hyperthyroidism.

The 17 normal individuals ranged in age from 22 to 54 years, with a mean age of 34.4 years. The 13 hyperthyroid individuals had an age range from 18 to 54 years, and a mean age of 26.6 years. All subjects were fasting for at least 8 hours prior to study. No attempt was made to modify the ward diet in the days preceding the study. The patients in both groups were sedated with Nembutal, 100 mg., or demerol, 50 mg., to obtain a reasonably basal state. Catheterization of the coronary sinus was carried out in the right anterior oblique position[6] and an indwelling needle inserted in either the radial or brachial artery. Coronary blood flow was determined by the nitrous oxide method of Kety and Schmidt as modified for the heart, utilizing the saturation technic and a coefficient of 1.1 for the partition of nitrous oxide between myocardium and blood.[7]

Just prior to the onset of nitrous oxide administration, blood was drawn simultaneously from the coronary sinus and a peripheral artery for oxygen, carbon dioxide, glucose, lactic acid, and pyruvic acid determinations, and for the nitrous oxide blood blanks. In addition to an integrated sample over the first minute of nitrous oxide administration, 5 other samples were collected during the first 5 minutes and 45 seconds of nitrous oxide administration, and a total of 8 samples of blood were obtained from the artery and coronary sinus over a period of 9 minutes

and 15 seconds of nitrous oxide administration. Samples were collected at as constant a rate as possible over a 30-second interval; the midpoint of each collection period was plotted as a discrete point. In order to compensate for the varying dead space of different size catheters, the volume of each catheter used was measured and this volume cleared from the catheter and discarded prior to each sampling of blood from the coronary sinus for nitrous oxide determination. The sampling from the coronary sinus catheter was so timed as to correct for the dead space of the particular catheter, so that the bloods collected for analysis represented true simultaneous sampling of arterial and coronary sinus blood. Arterial blood was obtained directly from the needle, no intervening tube being used.

While coronary flow studies were attempted in 17 normal and 13 hyperthyroid patients, the nitrous oxide curves were satisfactory in all aspects in only 8 normal and 5 hyperthyroid patients. Studies were rejected because of one or more of the following reasons: obvious deviation from a steady state during the study; failure of the venous and arterial curves to reach equilibrium; and irregularities in either the venous or arterial curve which precluded the construction of a smooth curve.

Cardiac output, utilizing the Fick principle, was determined either with right atrial blood obtained from the proximal lumen of a double-lumen catheter (distal lumen in coronary sinus), or with pulmonary artery blood as the mixed venous sample either just after or just before the start of the coronary blood flow. Attempts were made to determine cardiac output and coronary blood flow at as close an interval as possible. Oxygen consumption was determined by analysis of expired air and room air for oxygen on a Pauling oxygen analyzer. Corrections were not made for the paramagnetic effect of nitrous oxide on the Pauling oxygen analyzer, since in our experience the small amount of nitrous oxide present in the expired air introduced no significant error in the calculation of oxygen consumption. Mean pressures were obtained by electric integration, using Sanborn electromanometers and recorded on a Sanborn polyviso.

Blood gas analyses were carried out the day of study. Bloods for oxygen and carbon dioxide were analyzed in duplicate by the method of Van Slyke and Neil.[8] Nitrous oxide was determined as described by Kety.[9] Blood concentrations of glucose, lactic acid, and pyruvic acid were determined in duplicate, using the methods of Somogyi,[10] Barker and Summerson,[11] and Friedemann and Haugen,[12] respectively.

The oxygen consumption per 100 Gm. left ventricle/min. was obtained as follows:

$$\text{O}_2 \text{ consumption (ml./100 Gm. left ventricle/min.)} = [\text{arterial } \text{O}_2 \text{ content (vol. \%)} - \text{coronary sinus } \text{O}_2 \text{ content (vol. \%)}] \times \text{coronary flow (ml./100 Gm./min.)}$$

The coronary blood flow per 100 Gm. left ventricle/min. expressed as per cent of cardiac output was calculated as follows:

$$\text{Per cent of cardiac output} = \frac{\text{coronary flow (ml./100 Gm./min.)}}{\text{cardiac output (ml./min)}} \times 100$$

The myocardial oxygen consumption per 100 Gm. left ventricle/min. expressed as per cent of total oxygen consumption per minute was calculated as follows:

$$\text{Per cent of total } \text{O}_2 \text{ consumption} = \frac{\text{myocardial } \text{O}_2 \text{ consumption (ml./100 Gm./min)}}{\text{total } \text{O}_2 \text{ consumption (ml./min)}} \times 100$$

The coefficient of extraction of oxygen and the metabolites were obtained with the following equation:

$$\text{Coefficient of extraction (\%)} = \frac{\text{arterial level/100 ml.} - \text{coronary sinus level/100 ml.}}{\text{arterial level/100 ml.}} \times 100$$

Coronary vascular resistance was calculated as follows:

$$\text{Coronary vascular resistance (mm. Hg/ml./100 Gm./min.)} = \frac{\text{mean arterial pressure (mm. Hg)}}{\text{coronary flow (ml./100 Gm./min.)}}$$

The work of the left ventricle against pressure was expressed as follows:

$$\text{Left ventricular work (kilogram-meters-minute)} = \text{cardiac output (ml./minute)} \times \text{mean arterial pressure (mm. Hg)} \times 13.6$$

The contribution of lactic acid, pyruvic acid, and glucose to the aerobic metabolism of the left ventricle was indicated by converting the arterial-coronary sinus difference of these metabolites to their energy equivalents. The factors used to indicate the milliliters of oxygen necessary to metabolize 1 mg. of each metabolite were 0.75 for glucose and lactic acid and 0.67 for pyruvic acid.

The energy equivalent for glucose, for example, would then be calculated as follows:

$$\text{Energy equivalent for glucose (\%)} = \frac{\text{glucose arterial-coronary sinus difference (mg. \%)} \times 0.75}{\text{oxygen arterial-coronary sinus difference (Vol. \%)}} \times 100$$

The per cent of the oxygen difference across the myocardium accounted for by glucose, lactic acid, and pyruvic acid was determined by adding the individual energy equivalents.

Results

As expected, the cardiac output in the hyperthyroid group was higher than in the normal group, the mean for the 2 groups being 11.70 L./min. and 6.01 L./min., respectively (tables 1 and 2).

The mean coronary blood flow in the hyperthyroid group was 155 ml./100 Gm. left ventricle/min., compared to a mean of 103 ml./100 Gm./min. in the 8 normal individuals. One hyperthyroid individual (L.R.) had a coronary blood flow which fell within the normal range (table 2). The increased left ventricular coronary flow in the hyperthyroid group appeared to represent no greater proportion of the cardiac output than did the coronary flow among the normal patients. This is shown in tables 1 and 2, and is illustrated in figure 1, where the coronary flow for both groups is plotted against the per cent of cardiac output that each flow represents.

The mean coefficient of oxygen extraction by the myocardium was essentially similar in both groups although the oxygen A-V difference across the myocardium tended to be lower in the hyperthyroid group. This reflected a somewhat lower hemoglobin concentration in the latter group. However, in no patient was the hemoglobin reduced to levels below 9 Gm. per cent. It is not until the hemoglobin drops below the latter figure that there appears to be an effect on myocardial hemodynamics.[1]

The mean myocardial oxygen consumption among the hyperthyroid patients was 13.3

Table 1.—*Coronary Blood Flow and Myocardial Oxygen Consumption in Eight Normal Individuals*

Pt.	Age	Cardiac output (ml./min.)	Arterial coronary sinus O_2 A-V difference (Vol. %)	O_2 Coefficient of extraction (%)	Coronary blood flow (ml./100 Gm./min.)	Coronary blood flow per 100 Gm./min. as % of Cardiac output (%)	Body O_2 consumption (ml./min.)	Myocardial O_2 consumption (ml./100 Gm./min.)	Myocardial O_2 consumption per 100 Gm./min. as % of total O_2 consumption (%)	Mean arterial pressure (mm. Hg)	Coronary vascular resistance (mm.Hg/ml./100 Gm./min.)	Left ventricular work (Kg.M/min.)
J.R.	45	3250	12.3	69.8	95	2.9	224	11.7	5.2	93	0.98	4.2
L.H.	25	7250	10.1	61.2	129	1.8	261	13.0	4.9	83	0.64	8.2
J.S.	36	7480	10.8	70.9	68	0.9	243	7.3	3.0	90	1.3	9.2
R.M.	34	5180	10.8	72.3	91	1.8	159	9.8	6.1	106	1.2	7.4
G.D.	54	4380	6.7	49.8	101	2.3	162	6.8	4.2	92	0.91	5.5
F.B.	27	5620	11.1	66.8	129	2.3	219	14.3	6.5	120	0.92	9.2
C.S.	46	8250	10.6	68.3	98	1.2	245	10.4	4.2	95	0.97	10.7
S.N.	24	6680	9.6	57.0	113	1.7	191	10.6	5.3	98	0.85	8.9
Averages..	36.4	6011	10.3	64.5	103	1.9	213	10.5	4.9	97	0.97	7.9

Table 2.—*Coronary Blood Flow and Myocardial Oxygen Consumption in Five Hyperthyroid Individuals*

Pt.	Age	Cardiac output (ml./min.)	Arterial coronary sinus O_2 A-V difference (Vol. %)	O_2 Coefficient of extraction (%)	Coronary blood flow (ml./100 Gm./min.)	Coronary blood flow per 100 Gm./min. as % of cardiac output (%)	Body O_2 consumption (ml./min.)	Myocardial O_2 consumption (ml./100 Gm./min.)	Myocardial O_2 consumption per 100 Gm./min. as % of total O_2 consumption (%)	Mean arterial pressure (mm. Hg)	Coronary vascular resistance (mm.Hg/ml./100 Gm./min.)	Left ventricular work (Kg.M/min.)
M.M.	54	7300	9.7	62.0	154	2.1	246	14.9	6.1	115	0.75	11.8
J.J.	24	13600	8.6	64.8	168	1.2	331	14.4	4.3	90	0.53	16.7
J.B.	43	13820	7.0	59.3	157	1.1	238	11.0	4.6	80	0.51	15.0
L.R.	32	14930	10.2	60.7	117	0.78	397	11.9	3.0	76	0.65	13.6
M.H.	41	8870	7.9	68.1	180	2.3	228	14.2	6.2	98	0.54	11.8
Averages	38.8	11704	8.7	62.6	155	1.5	288	13.3	4.8	92	0.60	13.1

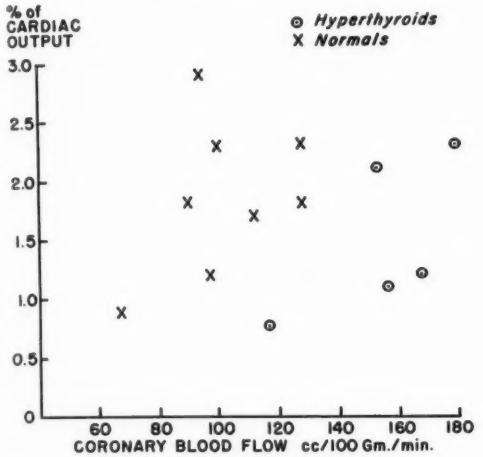


FIG. 1. The relationship between the coronary blood flow and per cent of cardiac output that each flow represents.

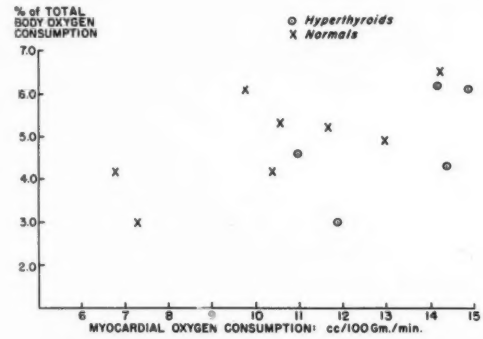


FIG. 2. The relationship between the myocardial oxygen consumption and per cent of total body oxygen consumption that each determination represents.

ml./100 Gm./min., compared to a mean of 10.5 ml./100 Gm./min. in the normal group. There tended to be considerable overlapping between the 2 groups. Figure 2 illustrates the relationship between the myocardial oxygen consumption and total body oxygen consumption. There appears to be no difference between the 2 groups in the range of scatter when the myocardial oxygen consumption is related to total, body oxygen consumption.

The coronary vascular resistance in the hyperthyroid group was lower, in almost all cases, than among the normal individuals, suggesting a vasodilatation of the coronary vasculature in the former group.

The myocardial carbohydrate metabolism was studied in a total of 17 normal and 13 hyperthyroid individuals (tables 3 and 4). There was no statistically significant difference in carbohydrate metabolism between the 2 groups. A value for p of 0.08 or greater was found when the following categories were compared: arterial glucose, lactic acid, and pyruvic acid; energy equivalent for glucose, lactic acid, and pyruvic acid; per cent of total oxygen A-V difference accounted for by carbohydrate metabolites; and lactic acid/pyruvic acid ratio.

The mean arterial glucose was identical in 2 groups, 76 and 75 mg. per cent, among the normal and hyperthyroid individuals, respectively. The range of variation of arterial glucose was narrow, 49 to 90 mg. per cent in the normal and 62 to 88 mg. per cent in the hyperthyroid individuals. Excluding the individual (F.B., table 3) with an arterial glucose of 49 mg. per cent, the range in the normal was 64 to 90 mg. per cent. Both the arterial-coronary sinus glucose difference and the coefficient of extraction for glucose showed considerable variation within both groups, with no difference between the groups. The mean extraction of glucose was small, averaging 4.9 per cent among the normal group and 4.8 per cent in the hyperthyroid group. Although there was a marked variation among individuals within both groups in the per cent of the oxygen A-V difference across the myocardium accounted for by glucose, the mean energy equivalent for glucose averaged close to 25 per cent for both groups. In neither group was there a correlation between the arterial glucose level and either the A-V difference of glucose across the myocardium, the glucose coefficient of extraction, or the glucose energy equivalent.

Lactic acid metabolism in the normal and hyperthyroid groups also showed striking similarities. In both groups, the mean extraction of lactic acid was about 33 per cent of the arterial level. The per cent of the simultaneously observed oxygen A-V difference across the myocardium accounted for by lactic acid

TABLE 3.—*Myocardial Carbohydrate Metabolism in Seventeen Normal Individuals*

Pt.	Glucose Metabolism				Lactic Acid Metabolism				Pyruvic Acid Metabolism				% Of Arterial-coronary sinus O_2 A-V difference accounted for by glucose, lactic acid, pyruvic acid	Arterial lactic acid: pyruvic acid ratio
	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %		
A.N.	69	0	0	0	10.2	3.6	35.3	28.6	1.26	0.49	38.8	3.8	32.4	7.7
L.B.	64	6	9.4	35.2	3.2	2.3	71.7	14.5	1.05	0.32	30.4	1.7	51.4	2.9
F.B.	49	14	28.6	93.4	8.5	5.6	65.8	38.1	1.03	0.43	41.7	2.4	134.2	8.5
E.S.	64	7	10.9	45.7	6.6	4.8	72.7	31.3	0.89	0.36	40.4	2.0	79.1	7.3
L.H.	64	−12	0	0	8.2	5.7	69.5	42.4	0.74	0.24	32.4	1.4	43.9	11.7
G.D.	77	8	10.4	89.6	6.3	2.6	41.2	29.1	1.09	0.56	51.3	4.8	123.0	5.7
R.B.	77	0	0	0	12.1	−3.7	0	0	0.80	0.24	30.0	1.7	1.7	15.0
R.M.	88	7	8.1	48.7	6.0	0	0	0	0.56	0.15	26.8	0.9	49.6	10.0
J.S.	80	6	7.5	41.8	19.3	6.4	33.2	44.5	1.40	0.67	48.0	4.1	90.4	14.0
G.M.	77	7	9.0	38.3	12.8	0.7	5.4	3.8	1.20	0.33	27.5	1.8	44.0	10.7
A.L.	90	−1	0	0	5.4	3.0	55.5	17.2	0.80	0.28	35.0	1.4	18.6	6.7
E.S.	75	−1	0	0	7.8	2.1	26.9	14.1	0.88	0.06	6.8	0.4	14.5	8.7
C.S.	86	−4	0	0	2.5	1.9	76.0	13.5	0.90	0.70	77.0	4.3	17.8	2.8
H.V.	77	−3	0	0	14.5	0.8	5.5	5.8	0.95	0.27	28.4	1.6	7.4	14.5
S.N.	85	0	0	0	4.8	0.1	2.0	0.8	0.69	0	0	0	0.8	7.0
J.R.	87	0	0	0	4.5	0.9	2.0	5.5	0.73	0	0	0	5.5	6.4
C.M.	76	0	0	0	3.5	1.1	31.4	7.3	0.72	0	0	0	7.3	4.9
Averages	76	3†	4.9	23.1	8.0	2.4†	34.9	17.4	0.91	0.30	30.2	1.9	39.0*	8.5

* In computing average, all values greater than 100% were considered to be 100%.
† All negative values considered as 0 in computing average.

TABLE 4.—*Myocardial Carbohydrate Metabolism in Thirteen Hyperthyroid Individuals*

Pt.	Glucose Metabolism				Lactic Acid Metabolism				Pyruvic Acid Metabolism				% of arterial-coronary sinus O_2 A-V difference accounted for by glucose, lactic acid, pyruvic acid	Arterial lactic acid: pyruvate acid ratio
	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %	Arterial level mg. %	Arterial-coronary sinus A-V difference mg. %	Coefficient of extraction %	Energy equivalent %		
I.B.	85	3	3.5	21.1	12.0	3.6	30.0	24.7	1.56	0.32	20.5	1.9	47.7	7.6
A.J.	78	0	0	0	4.8	2.7	56.2	19.9	0.78	0.46	58.9	3.0	22.9	6.2
V.H.	73	3	4.1	24.5	5.4	2.3	42.6	18.7	0.90	0.27	30.0	1.9	45.1	6.0
I.M.	80	0	0	0	9.2	2.6	28.2	20.5	1.34	0.33	24.6	2.2	22.7	6.7
E.H.	74	1	1.4	6.6	7.1	3.5	50.0	27.3	1.19	0.16	13.4	1.0	34.9	5.9
W.S.	70	8	11.4	52.6	6.0	3.2	53.3	21.1	1.31	0.33	25.1	1.8	75.5	4.6
B.P.	62	12	19.3	95.1	2.4	0.5	20.8	4.0	0.97	0.41	42.2	2.9	102.0	2.5
F.R.	74	6	8.1	44.6	5.4	2.3	42.6	16.9	1.01	0.31	30.7	1.6	63.1	5.3
L.R.	70	2	2.8	16.2	5.0	1.5	30.0	12.2	1.12	0.41	36.6	2.8	31.2	4.4
L.R.	86	3	3.5	22.1	12.5	1.4	11.2	10.3	0.89	0.41	47.2	2.8	35.2	14.0
M.M.	88	1	1.1	7.8	4.8	−1.8	0	0	0.36	−0.18	0	0	7.8	13.3
J.B.	70	5	7.1	53.8	6.0	2.4	40.0	25.8	1.01	0.32	31.6	3.1	82.7	5.9
J.J.	67	−10	0	0	2.1	−0.3	0	0	0.76	−0.02	0	0	0	2.8
Averages	75	3†	4.8	26.5	6.4	2.0†	31.1	15.5	1.01	0.28†	27.7	1.9	43.7*	6.6

* In computing average, all values greater than 100% were considered to be 100%.
† All negative values considered as 0 in computing average.

veraged, in both groups, somewhat less than hat accounted for by glucose, the energy quivalent for lactic acid averaging 17.4 and 5.5 per cent among the normal and hyperhyroid groups, respectively. As with glucose, here was no relation between the arterial actate level and lactic acid utilization by the myocardium.

The pyruvic acid usage by the myocardium n the normal and hyperthyroid patients was lso similar. The arterial level in both groups was low, averaging close to 1 mg. per cent. The energy equivalent for pyruvic acid was negligible in both groups, averaging an identical 1.9 per cent.

In neither group was there a relationship between the arterial level of one metabolite and the arterial-coronary sinus difference, coefficient of extraction, or energy equivalent of the other metabolites.

It is of interest that the ratio of arterial lactic acid to arterial pyruvic acid showed similar ranges in both groups (tables 3 and 4), and averaged less than the previously described ratio of 12.2 in normal human subjects.[13] The lactic acid levels in the hyperthyroid group tended to be lower than in the normal group, averaging 6.4 mg. per cent in the former and 8.0 mg. per cent in the latter group. The mean arterial pyruvate levels were similar in both groups, averaging 1.01 mg. per cent in the hyperthyroid and 0.91 mg. per cent in the normal group. These findings militate strongly against the presence of thiamine deficiency among the hyperthyroid patients.[13]

Discussion

The findings in this report indicate that the coronary flow per unit of left ventricular weight is elevated in hyperthyroidism. The increased coronary flow in this disease appears to represent no greater proportion of the simultaneously determined cardiac output than does the coronary flow in normal individuals. Although, as indicated in figure 1, the relationship between coronary flow and cardiac output is not linear in either group, the range of scatter is similar in both groups. No attempt is made to infer that the coronary flow is increased as a result of the increased cardiac output in hyperthyroidism. Both these parameters may be altered by a common factor.

The myocardial oxygen consumption in the 2 groups showed considerable overlapping. However, as previously illustrated, there appeared to be no difference between the 2 groups when the myocardial oxygen consumption was related to total body oxygen consumption (figure 2), indicating that the myocardial oxygen consumption in hyperthyroidism represents the same percentage of whole-body oxygen consumption as in the normal group. This increased myocardial oxygen usage in hyperthyroidism appears to be brought about by an increased coronary blood flow in the presence of a normal percentage extraction of arterial oxygen by the myocardium.

The above results are in agreement with those of Rowe and associates,[14] who found the coronary flow and myocardial oxygen consumption elevated prior to surgery in a group of hyperthyroid individuals. Bing[1] reported only a slight increase in coronary blood flow in hyperthyroidism and a lower than normal myocardial oxygen consumption. Satisfactory explanation for such discrepancies is not readily apparent.

Conflicting results have been reported on the effect of thyroid substances on the heart of experimental animals. These inconsistencies are probably related to the use of various types of preparations and the study of different anatomic regions of the heart. Ulrick and Whitehorn[2] reported a significant increase in oxygen consumption of both atrial and ventricular tissue of the hyperthyroid rat in vitro, the former tissue showing a greater change than the latter. Dock and Lewis,[15] utilizing the heart-lung preparation of the rat, found that the increase in myocardial oxygen consumption of the hyperthyroid rat was entirely explicable on the basis of the increased heart weight and rate. Leblond and Hoff[16] reported an increased heart rate produced by thyroxin in the intact thyroidectomized rat. These authors did not measure myocardial oxygen consumption. Gordon and Heming,[17] using minced or sliced heart muscle of the hyperthyroid rat, could show only a transient increase in myocardial oxygen consumption followed by a depression.

McEachern,[3] who was able to demonstrate an increased oxygen consumption of the intact atrium of the hyperthyroid guinea pig in vitro, also found an increase in oxygen consumption followed by a depression when using minced or sliced atrial tissue obtained from the hyperthyroid guinea pig, suggesting that the use of sliced or minced tissue may give misleading results.

The mean coronary blood flow of 103 ml./100 Gm./min. in the normal group in this study is comparable to a mean flow of 96 ml./100 Gm./min. found by Goodale and Hackel[18] in 4 normal human beings. The range in their subjects was 91 to 103 ml./100 Gm./min., compared to a range of 68 to 129 ml./100 Gm./min. in the present study. Bing[1] has reported a somewhat lower mean coronary blood flow of 77 ml./100 Gm./min. among normal subjects. He found a mean myocardial oxygen consumption of 9.4 ml./100 Gm./min., compared to a higher mean figure of 10.5 ml./100 Gm./min. among the 8 normal persons in this series.

Discrepancies between the value of coronary flow in the normal subjects in this series and those reported by other authors may be accounted for by differences in technic. If corrections for dead space existing in the coronary sinus catheter are not made, but samples are drawn simultaneously from artery and coronary sinus without such correction, the determined coronary sinus nitrous oxide concentration will be lower than actually existing in the coronary sinus blood at a given instant, particularly during the first portion of the curve where rapid changes in nitrous oxide concentrations are occurring. This will tend to widen the arteriovenous difference of nitrous oxide and consequently make the calculation of coronary flow falsely low. We have used the saturation technic throughout, finding little advantage or convenience in the desaturation method. The results by both these technics are comparable.[18]

As previously demonstrated, the study of the carbohydrate metabolism in the normal and hyperthyroid patients revealed great similarity, and there was very little pattern that could be deduced from the results obtained. Certainly on the basis of, and within the limitations of, the present studies, there is no abnormality of the myocardial carbohydrate metabolism in hyperthyroidism. As others have found in man[19] and dogs,[20] the heart is capable of utilizing glucose, pyruvic acid, and lactic acid. The contribution of the latter two metabolites to the aerobic metabolism of the heart is sharply restricted by their relatively low arterial levels. Usage of glucose appears to be variable, and the total contribution of the sum of the three metabolites studied to the aerobic metabolism of the heart varied markedly (figures 3 and 4). The respiratory quotient also showed considerable variation and, in our hands, in no way appeared to correlate with the degree of carbohydrate usage. Respiratory quotient for each patient is shown above the appropriate bar graph in figures 3 and 4.

No relationship could be demonstrated between the usage of one metabolite and the utilization of any other. There was no correlation between the work of the left ventricle and the carbohydrate usage. These findings are in conformity with those previously reported by Bing[19] and by Goodale and Hackel.[20] A relationship could not be demonstrated between the arterial level of any of the metabolites and their extraction by the myocardium, results which are in disagreement with the previously quoted authors. However, the range of the arterial concentration of the metabolites, especially glucose, was relatively narrow in the present study. No attempt was made to raise

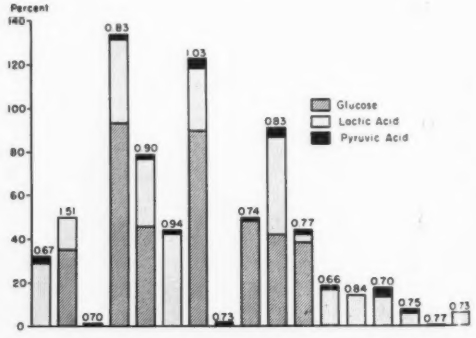


FIG. 3. Normal subjects. The per cent of the arterial-coronary sinus oxygen difference across the myocardium accounted for by glucose, lactic acid, pyruvic acid. Height of bar represents sum of contribution of these metabolites. Figure above each bar refers to myocardial respiratory quotient.

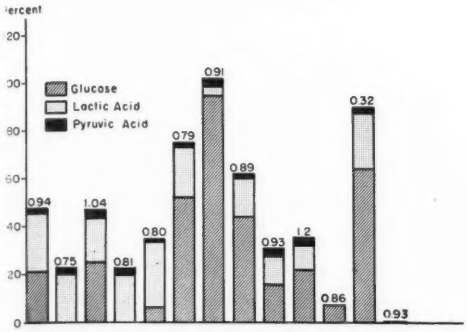


FIG. 4. Hyperthyroid patients. The per cent of the arterial-coronary sinus oxygen difference across the myocardium accounted for by glucose, lactic acid, pyruvic acid. Markings same as figure 3.

acutely the blood level of any of the metabolites. In other studies,[21] in which the arterial lactic and pyruvic acid concentrations were rather markedly increased by fructose administration, there occurred an increased extraction of these metabolites by the myocardium. Though the greater uptake tended to be associated with the higher blood levels, this relationship was not linear.

It would appear to us that the nutritional state of the body, which is not necessarily reflected in the arterial level of the carbohydrate substances measured in this study, would be of importance in determining the metabolism of the myocardium. It may be that this factor as well as the arterial level of the metabolites is important in determining uptake by the myocardium. According to Peters,[22] after an overnight fast, 60 per cent of the energy of the body is provided by fat. That the human myocardium can utilize fat and ketones has been amply demonstrated.[23] At any rate, it is of interest that on a routine ward diet and following only an overnight fast, considerable part or all of the metabolism of the left ventricle may be provided for by substances other than carbohydrates.

Some of the cases in both groups in the present study had a negative arterial-coronary sinus difference across the myocardium for the various metabolites studied. In several cases, the negative A-V difference was small and probably within the error of the method of determination. However, in some cases it does not appear to be explicable on this basis. We can offer no explanation of these findings at this time.

Perhaps there is no disease in which the effects on the component parts of the circulation in the human being have been studied so carefully as in hyperthyroidism. Our data and that of others[24] indicate that in the majority of cases of hyperthyroidism, although the cardiac output is elevated, the over-all arteriovenous oxygen difference is normal. Studies of the component parts of the circulation give varying results. The response of the heart in hyperthyroidism with increased output and normal arteriovenous oxygen difference is the result of a high skin and muscle flow,[25] and probably of diminished oxygen A-V difference in these areas; of a normal splanchnic flow and high splanchnic oxygen A-V difference with a resultant high splanchnic oxygen consumption[24]; of a normal cerebral blood flow; of oxygen A-V difference and oxygen consumption[26]; of a normal renal blood flow[27]; and, as reported here, of a high coronary blood flow, normal arterial-coronary sinus oxygen difference, and increased myocardial oxygen consumption. In all probability, in other states in which high cardiac output is present, considerable regional differences in hemodynamics exist.

The needs of the heart in hyperthyroidism appear to be met in the same fashion as in other situations in which cardiac output is increased. As a result of exercise, the nonfailing heart responds in similar fashion to the hyperthyroid heart, i.e., increase in coronary blood flow, decrease in coronary vascular resistance, unchanged arterial-coronary sinus oxygen difference, and increase in myocardial oxygen consumption.[28] Similar findings are reported in the case of peripheral arteriovenous fistula.[1] In severe anemia, in which case the cardiac output is almost always high, both the coronary blood flow and myocardial oxygen consumption are elevated.[1]

Thus, in terms of its carbohydrate metabolism and its myocardial hemodynamics, there appears to be nothing unique about the heart in hyperthyroidism. An important question

that remains to be answered is what regulates the response of the heart to an increased work load. Hypertension, the most common cardiovascular abnormality in which the work of the left ventricle is increased, is apparently not accompanied by either an increase in coronary blood flow or myocardial oxygen consumption per 100 Gm. left ventricle.[29] The meager data available indicate that no change in coronary blood flow or myocardial oxygen consumption accompanies aortic stenosis, while in coarctation of the aorta and aortic insufficiency both these parameters are increased.[29] Reasons and mechanisms for these reported differences in myocardial hemodynamics are obscure.

Summary

In a series of 5 hyperthyroid patients, the mean coronary blood flow and myocardial oxygen consumption/100 Gm. left ventricle/min. averaged 155 and 13.3 ml. respectively. The corresponding values in 8 normal patients were 103 and 10.5 ml. The coefficient of oxygen extraction across the myocardium was similar in both groups.

The per cent of total cardiac output and oxygen consumption accounted for by the heart was similar in both groups.

On the basis of studies performed on 17 normal and 13 hyperthyroid patients, it is concluded that the myocardial metabolism of glucose, lactic acid, and pyruvic acid does not deviate from the normal among hyperthyroid patients.

Usage of carbohydrate substances showed marked and unexplained variations in both groups. No relationship between the arterial level of a metabolite and its myocardial extraction could be demonstrated. The oxygen A-V difference across the myocardium accounted for by the sum of all the metabolites studied averaged 39 per cent among the normal and 43.7 per cent among the hyperthyroid patients.

On the basis of studies of myocardial hemodynamics and carbohydrate metabolism there appears to be no unique effect of thyroid hormone on the heart.

Acknowledgment

We wish to express our thanks to the following laboratory technicians who at one time or another aided in this work: Mrs. Barbara Rinkenberger, Mrs. Nancy Davenport, Mrs. Karen Massel, Miss Ann-Marie Sundin, and Mrs. Shirley Loy.

Summario in Interlingua

In un serie de 5 patientes hyperthyroide, le valor median del fluxo de sanguine coronari e del consumption myocardial de oxygeno per 100 g ventriculo sinistre per minuta esseva medianmente 155 e 13,3 ml, respectivemente. Le valores correspondente in 8 normal patientes esseva 103 e 10,5 ml. Le coefficiente de extraction oxygenic a transverso le myocardio esseva simile in le duo gruppos.

Le procentage del total rendimento cardiac e del total consumption oxygenic attribuibile al corde esseva simile in le duo gruppos.

Super le base de studios executate in 17 normal e 13 hyperthyroide patientes, nos conclude que le metabolismo myocardial de glucosa, acido lactic, e acido pyruvic in patientes hyperthyroide non devia ab le norma.

Le uso de substantias de hydrato de carbon exhibiva marcate sed inexplicate variationes in le duo gruppos. Il non esseva possibile demonstrar un relation inter le nivello arterial de un metabolito e su extraction myocardial. Le differentia atrio-ventricular de oxygeno a transverso le myocardio que esseva explicabile per le summa del metabolitos studiate amontava medianmente a 39 pro cento inter le patientes normal e a 43,7 pro cento inter le hyperthyroides.

Super le base de nostre studios del hemodynamica myocardial e del metabolismo de hydratos de carbon il pare justificate concluder que il existe nulle specific effecto de hormon thyroide super le corde.

REFERENCES

1. Bing, R. J.: The coronary circulation in health and disease as studied by coronary sinus catheterization. Bull. New York Acad. Med. **27:** 407, 1951.
2. Ulrick, W. C., and Whitehorn, W. V.: Influence of thyroid hormone on respiration of cardiac tissue. Am. J. Physiol. **171:** 407, 1952.
3. McEachern, D.: Direct measurements of the oxygen consumption of isolated beating auricles

from normal and thyrotoxic guinea pigs. Bull. Johns Hopkins Hosp. **50:** 287, 1932.

SHELLEY, W. B., CODE, C. E., AND VISSCHER, M. B.: Influence of thyroid, dinitrophenol and swimming on glycogen and phosphocreatine levels of rat heart in relation to cardiac hypertrophy. Am. J. Physiol. **138:** 652, 1942.

TALMERS, F. N., REGAN, T. J., DEFAZIO, V., LEIGHT, L., AND HELLEMS, H. K.: The effects of hyperthyroidism on the circulatory system. Abstracted, Clin. Res. Proc. **3:** 120, 1955.

[6] GOODALE, W. T., LUBIN, M., ECKENHOFF, S. E., HAFKENSCHIEL, J. H., and BANFIELD, W. G.: Coronary sinus catheterization for studying coronary blood flow and myocardial metabolism. Am. J. Physiol. **152:** 340, 1948.

[7] ECKENHOFF, J. E., HAFKENSCHIEL, J. H., HARMEL, M. H., GOODALE, W. T., LUBIN, M., BING, R. J., AND KETY, S. S.: Measurement of coronary blood flow by the nitrous oxide method. Am. J. Physiol. **152:** 356, 1948.

[8] VANSLYKE, D. D., AND NEIL, J. M.: Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[9] KETY, S. S.: Methods in Medical Research. Volume I, Chicago, the Year Book Publishers Inc., 1948, p. 209–210.

[10] SOMOGYI, M.: Determinations of blood sugar. J. Biol. Chem. **160:** 69, 1945.

[11] BARKER, S. B., AND SUMMERSON, W. H.: The colorimetric determination of lactic acid in biological material. J. Biol. Chem. **138:** 535, 1948.

[12] FRIEDEMANN, T. E., AND HAUGEN, G, E.: Pyruvic acid determination of keto acids in blood and urine. J. Biol. Chem. **147:** 415, 1943.

[13] CHESLER, A., HOMBURGER, E., AND HIMWICH, H.: Carbohydrate metabolism in vitamin B_1 deficiency. J. Biol. Chem. **153:** 219, 1944.

[14] ROWE, G. G., HUSTON, J. H., WEINSTEIN, A. B., AND CRUMPTON, C. H.: Coronary blood flow, cardiac work, and myocardial metabolism in thyrotoxicosis. Abstracted, J. Lab. & Clin. Med. **44:** 921, 1954.

[15] DOCK, W., AND LEWIS, S. K.: The effect of thyroid feeding on the oxygen consumption of the heart and of other tissues. J. Physiol. **74:** 401, 1932.

[16] LEBLOND, C. P., AND HOFF, H. E.: Comparison of cardiac and metabolic actions of thyroxine, thyroxine derivatives, and dinitrophenol in thyroidectomized rats. Am. J. Physiol. **141:** 32, 1944.

[17] GORDON, E. S., AND HEMING, A. E.: The effect of thyroid treatment on the respiration of various rat tissues. Endocrinology **34:** 353, 1944.

[18] GOODALE, W. T., AND HACKEL, D. B.: Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. Circulation Research **1:** 511, 1953.

[19] BING, R. J., SIEGEL, A., VITALE, A., BALBONI, F., SPARKS, E., TAESCHLER, M., KLAPPER, M., AND EDWARDS, S.: Metabolic studies on the human heart in vivo. I. Studies on carbohydrate metabolism of the human heart. Am. J. Med. **15:** 284, 1953.

[20] GOODALE, W. T., AND HACKEL, D. B.: Myocardial carbohydrate metabolism in normal dogs with effects of hyperglycemia and starvation. Circulation Research **1:** 509, 1953.

[21] DEFAZIO, V., HELLEMS, H. K., LEIGHT, L., TALMERS, F. N., AND REGAN, T. J.: The effects of fructose on myocardial metabolism. Abstracted, J. Lab. & Clin. Med. **44:** 786, 1955.

[22] PETERS, J. P.: Interrelationships of food stuffs. Ann. New York Acad. Sc. **56:** 127, 1952.

[23] BING, R. J., SIEGEL, A., UNGAR, I., AND GILBERT, M.: II. Studies on fat, ketone, and amino acid metabolism. Am. J. Med. **16:** 504, 1954.

[24] MYERS, J. D., BRANNON, E. S., AND HOLLAND, B. C.: A correlative study of the cardiac output and the hepatic circulation in hyperthyroidism. J. Clin. Invest. **29:** 1069, 1950.

[25] EICHNA, L. W., AND WILKENS, R. W.: Blood flow to the forearm and calf IV. Thyroid activity: observations on the relation of blood flow to basal metabolic rate. Bull. Johns Hopkins Hosp. **68:** 512, 1941.

[26] SCHEINBERG, P.: Cerebral circulation and metabolism in hyperthyroidism. J. Clin. Invest. **29:** 1010, 1950.

[27] CORCORAN, A. C., AND PAGE, I. H.: Specific renal functions in hyperthyroidism and myxedema. J. Clin. Endocrin. **7:** 801, 1947.

[28] LOMBARDO, T. E., ROSE, L., TAESCHLER, M., TULOY, S., AND BING, R. J.: The effect of exercise on coronary blood flow, myocardial oxygen consumption and cardiac efficiency in man. Circulation **7:** 71, 1953.

[29] BING, R. J., HAMMOND, M. M., HANDELSMAN, J. C., POWERS, S. R., SPENCER, F. C., ECKENHOFF, J. E., GOODALE, W. T., HAFKENSCHIEL, S. H., AND KETY, S. S.: The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. Am. Heart J. **38:** 1, 1949.

The Effect of Age on Mean Spatial QRS and T Vectors

By ERNST SIMONSON, M.D., AND ANCEL KEYS, PH.D.

The differentiation between normal and abnormal changes in conventional electrocardiography is substantially improved by consideration of normal age trends. For clinical application of spatial vectorcardiography, consideration of age trends is equally important. On the basis of statistical evaluation of magnitude, azimuth and elevation of mean spatial QRS and T vectors in 105 healthy young men and 178 healthy older men, upper and lower limits were determined for each age group. The age differences were highly significant for all items of vector analysis.

IN A previous study,[1] highly significant statistical differences in most conventional electrocardiographic items were found between a group of 157 normal men from 18 to 25 years and 233 men from 45 to 54 years. Consideration of age trends, of course, is as important for clinical application of spatial vectorcardiography as for conventional electrocardiography, and specific information appeared to be desirable.

The only study on changes of spatial QRS and T vectors with age is that by Abildskov,[2] who compared the maximum instantaneous QRS and T vector projections in the frontal and sagittal planes between 75 young adults (from 22 to 33 years) and 114 older subjects (from 40 to 73 years). The group means in some of the items were considered to be significantly different, but no statistical evaluation of the mean differences between the two age groups was made. Furthermore, the vector projections on single planes are very sensitive to positional variation. Rotation in the sagittal plane will affect the magnitude and angles of the vector projections in the frontal plane and vice versa, and the instantaneous maximum vectors in the two planes are not identical due to phase differences. Determination of spatial vectors in terms of azimuth, elevation, and magnitude, from their projections in two planes or electronically by means of the stereovector electrocardiographic system,[3] eliminates, at least theoretically, the effect of positional changes on magnitude, and also the direction is more precisely defined. Although the present methods of spatial-vector analysis fall somewhat short of this goal,[4] spatial vector analysis permits a synthesis of information that cannot be readily obtained from the conventional interpretation of single leads, and it also drastically reduces the number of items to be analyzed.

METHOD AND SUBJECTS

Mean spatial QRS and T vectors were constructed from conventional leads by means of a mechanical analyzer.[5] The data are given in terms of azimuth H° (left midaxillary line O°; midline front +90°; midline back −90°; right midaxillary line ±180°); elevation V° (angle between a vertical line through the hypothetical center and the vector (O° vertical down; 90° horizontal); vector magnitude (1 mm. = 0.1 mv.); and the angle between the mean spatial QRS and T vectors (dA°).

A group of 105 young men from 18 to 28 years was compared with a group of 178 older men in the sixth decade. Both groups were found to be clinically healthy in a thorough clinical examination that included ballistocardiography, blood chemistry, and physiologic stress tests.

The group of older men was identical with that used in previous studies of the effect of age on the conventional electrocardiogram[1] and the effect of relative body weight on mean spatial QRS and T vectors.[6] This group has been examined annually over a period of eight years and, therefore, provides a much better selection of clinically normal subjects than would be possible in a single check-up.

The younger group is not identical with that used in the previous study.[1] The selection of the younger group was made on the basis of only one examination, but the likelihood of latent cardiac pathology is, of course, much less than in an older age group.

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

This investigation was supported in part by research grants H-2071 from the National Heart Institute, U. S. Public Health Service, and the Minnesota Heart Association.

Results and Discussions

Table 1 shows the group means (M) and standard deviations (σ), of the younger (Y) and older (O) age group, the mean differences (Δ) and their statistical significance, evaluated by means of the t-test. The differences in the standard deviations between the two groups were evaluated by means of the F-test. The mean group differences (Δ) of all seven items of spatial vector analysis have high statistical significance. As compared to the younger age group, both vectors are rotated more anteriorly in the older men (azimuth H° more positive) by about the same degree. The higher elevation (V°) of the QRS and the T vector in the older men corresponds to the shift to the left of the QRS and T axes with age in the conventional electrocardiogram,[1] and also the greater elevation of the QRS vector than that of the T vector corresponds to a greater shift to the left of the Einthoven QRS axis than that of the T axis. Thus, highly significant age trends in adult population are apparent in the frontal plane of the limb leads as well as in the horizontal plane of the precordial leads.

The magnitude of the mean spatial QRS and the T vector is significantly smaller in the older men. This difference corresponds well with the lower amplitudes of R_2, T_2, ΣQRS and ΣT in the conventional electrocardiogram.[1]

Without providing direct experimental proof, Olbrich and Woodford-Williams[7] suggested that electrocardiographic age trends in single leads are due to anatomic changes in the thorax rather than to changes of the electric events in the heart. Positional factors are, indeed, of major importance for amplitudes in single leads, but are minimized in the determination of the magnitude of spatial vectors. Positional factors, therefore, cannot account for the large age differences of the spatial QRS and T vectors, and, on the basis of these results, it is also unlikely that they explain the decrease of the amplitudes with age in single leads. The distribution range of QRS-V°, T-V°, and T-dA° is larger in the older men, as shown by the significantly larger standard deviation. The standard deviation of QRS-Mag is significantly smaller in the older age group, but this is explained by the smaller mean value. The variability coefficient, σ/M is identical (30 per cent) for both age groups. The greater variability between individuals in the elevation (V°) of the QRS and T vector is not due to a more heterogeneous composition of the older group, which consisted of "whitecollar workers." If anything, the younger age group, consisting of students and soldiers, was more heterogeneous. The smaller magnitude and higher elevation of the mean spatial vectors in the older group is also reflected in the length and directions of the average maximum frontal and sagittal vector projections in Abildskov's material.

Table 1.—*Mean values (M) and standard deviations (σ) of Magnitude (Mag.) and Directions (H° = azimuth, V° = elevation, dA°, angle between QRS and T vectors) in a group of 105 young (Y) and 178 older (O) healthy men. The differences between the means (Δ) are evaluated by means of the t test, and the differences between the standard deviations by means of the F test.*

Group		QRS Vector			T Vector			dA°
		H°	V°	Mag. mm.	H°	V°	Mag. mm.	
Y	M	−31.2	28.4	12.5	33.6	53.2	4.1	47.3
	σ	21.6	21.0	3.8	13.6	15.2	1.2	15.3
O	M	−22.2	54.2	9.9	42.3	61.9	3.4	55.0
	σ	21.4	26.0	3.3	14.8	19.32	1.2	22.1
Δ	Y-O	9.0	25.8	−2.6	8.7	8.7	−0.68	7.7
t		3.42‡	8.62‡	−5.99‡	4.92‡	3.95‡	4.53‡	3.15†
F		1.027	1.531†	1.387*	1.199	1.628†	1.079	2.080†

* $p = < 0.05$
† $p = < 0.01$
‡ $p = < 0.001$

Abildskov considered the magnitude of the frontal and sagittal T loop to be similar in the younger and older men, but the 20 to 30 per cent lower magnitude in his older group is in the same order as our results, and might well have been statistically significant.

In contrast to our results, Abildskov found the average orientation of the T vector farther posteriorly in the older men. No satisfactory explanation for this discrepancy can be given, but several factors might be involved. It is unlikely that the discrepancy is due to a different definition of spatial vectors: mean vectors in this study and instantaneous maximum vectors in Abildskov's series. A high correlation between instantaneous maximum and mean vectors were found in a recent study.[8] Of greater importance may be the different lead system,[9] particularly since the location of the anteroposterior vector was determined by Abildskov from the sagittal plane projection and, in this study, from the horizontal plane projection, which appears to be more directly related to rotation around a vertical axis.

Table 2 shows the upper and lower limits for 95 per cent of the healthy male population as represented by the two age groups. The limits were calculated from the standard deviations, since the groups, particularly the younger group, are too small for analysis of possible skewness of distribution, and, therefore, the limits in table 2 have preliminary character. However, no major changes are expected in larger groups, and, in any case, the mean differences of table 1 are reliable. In the larger groups used for the evaluation of age trends in conventional electrocardiographic items,[1] means and median gave identical results. It is of interest that the differences between the upper limits of the angles are larger than those between the lower limits.

The limits could be conceivably narrowed and improved by consideration of the correlations between the QRS and T vector.

A large literature is concerned with the correlation between the QRS complex and the T wave; Katz[10] in his excellent review listed over 500 references as early as 1928. Due to the extreme sensitivity of single leads to positional variability, no consistent relationship could be established. The ventricular gradient, as another approach to this problem, was critically reviewed recently.[11]

In the older group there was a highly significant positive correlation for men with $dA^0 < 45^0$ ($r = 0.35$, $t = 2.84$, $p = 0.01$, $N = 56$) and for men with dA^0 from 45^0 to 65^0 ($r = 0.51$, $t = 4.5$, $p = <0.001$, $N = 68$), but not for those with $dA^0 > 65^0$ ($r = 0.18$, $N = 54$). The correlation for the total group of 178 men ($r = .358$) was of high statistical significance ($p = <.001$). The correlation between QRS-Mag and T-Mag was somewhat lower in the group of younger men ($r = 0.228$), but still statistically highly significant ($p = 0.01$).

The relationship between QRS-Mag and T-Mag can be expressed by the regression equations, calculated with the method of the least squares. The equations were T-Mag = 2.090 + 0.132 (QRS-Mag) for the older group, and T-Mag = 3.148 + 0.075 (QRS-Mag) for the younger group. The slope (0.132 and 0.075, respectively) was not significantly different in both groups. Although the correlation between QRS-Mag and T-Mag is statistically highly significant, it is too low to be used for individual prediction. In view of this situation, the ratio of the magnitude of the

TABLE 2.—*Upper and Lower Normal Limits for 95 per cent of a Healthy Population of Young (Y) and Older (O) Adults*

Group		QRS Vector			T Vector			dA°
		H°	V°	Mag. mm.	H°	V°	Mag. mm.	
Y	Upper	+11.1	69.6	19.9	60.3	83.0	6.5	77.3
	Lower	−73.5	0.0	5.1	6.9	23.4	1.7	17.3
O	Upper	+19.7	+105.2	16.9	71.4	99.8	5.8	98.3
	Lower	−64.0	3.2	3.5	13.2	24.0	1.0	11.7

QRS vector to that of the T vector (QRS-Mag:T-Mag) may be useful for evaluation of normality. It is essentially the same in the younger men (mean 3.28, S.D. ±1.14), and in the older men (mean 3.17, S.D. ±1.14), i.e., the decrease of the QRS vector magnitude with age parallels the decrease of the T vector magnitude.

There is good reason to believe that the electrocardiographic age trends in apparently healthy adult populations are related to the increasing arteriosclerosis of the coronary arteries. In Italian populations, the incidence of coronary artery disease as well as the electrocardiographic trends are much less pronounced. The mean group differences in electrocardiographic items between patients with an early phase of coronary artery disease (normal resting electrocardiogram, typical history of angina pectoris, abnormal exercise tolerance test) as compared to a healthy middle-aged population are in the direction of age trends in the same (Minnesota) population.[12] From this point of view, the angle (dA^0) between the mean spatial QRS and T vectors is of interest, since it increases in left ventricular strain or ischemia. It is, therefore, quite possible that the significantly larger angle dA^0 in the older men might be due to a mild degree of subclinical left ventricular ischemia.

Summary

Mean spatial QRS and T vectors, constructed from the conventional electrocardiogram, by means of a mechanical analyzer, were compared in 105 young healthy men from 18 to 28 years old and in 178 healthy older men in their sixth decade.

All items of vector analysis (magnitude, azimuth, elevation of the mean QRS and T vectors, and the angle between these vectors) showed highly significant differences between the group means.

In the older men, both the QRS and T vector were rotated more anteriorly (larger azimuth angle), and were more elevated, their magnitude was smaller, and the angle between the vectors was larger than in the younger men.

The range of interindividual variability was significantly larger in the older men for the angles of elevation of the QRS and the T vector.

Preliminary limits for 95 per cent of the healthy male population, corrected for age are calculated from the standard deviation.

Summario in Interlingua

Le median vectores spatial QRS e T, construite ab le electrocardiogramma conventional per medio de un analysator mechanic, esseva comparate in 105 normal masculos inter 18 e 28 annos de etate e in 178 normal masculos in le sexte decennio de lor vita.

Omne elementos del analyse vectorial (magnitude, azimut, elevation del median vectores QRS e T, e le angulo inter iste vectores) monstrava significativissime differentias inter le duo gruppos.

In le gruppo a etates plus avantiate, le vectores QRS e T esseva ambes rotate plus anteriormente (con un plus grande angulo azimutic) e plus elevate que in le gruppo del plus juvene subjectos. Le magnitude del vectores esseva reducite, e le angulo inter illos esseva plus grande.

In le gruppo a etates plus avantiate le variabilitate interindividual del elevation del angulos del vectores QRS e T esseva significativemente plus extense.

Es presentate le limites preliminari, calculate ab le deviation standard e corrigite pro le factor del etate, que es valide pro 95 pro cento del normal population mascule.

REFERENCES

[1] Simonson, E., and Keys, A.: The effect of age and body weight on the electrocardiogram of healthy men. Circulation **6:** 749, 1952.

[2] Abildskov, I. A.: A study of the spatial vectorcardiogram in normal subjects over the age of forty years. Circulation **12:** 268, 1955.

[3] Schmitt, O. H., and Levine, R. B.: Direct visual examination of stereovectorelectrocardiograms. Fed. Proc **11:** 140, 1952.

[4] —, and Simonson, E.: The present status of vectorcardiography. Arch. Int. Med. **96:** 574, 1955.

[5] Simonson, E.: A spatial vector analyzer for the conventional electrocardiogram. Circulation **7:** 403, 1953.

[6] —, AND KEYS, A.: The spatial QRS and T vector in 178 normal middle-aged men. Circulation **9:** 105, 1954.

[7] OLBRICH, O., AND WOODFORD-WILLIAMS, E.: The effect of change of body position on the precordial electrocardiogram in young and aged subjects. J. Gerontol. **8:** 56, 1953.

[8] SIMONSON, E., AND SCHMITT, O. H.: A comparison of spatial instantaneous electrocardiographic vectors as measured with the SVEC with mean vectors as derived from conventional ECG leads. Circulation Research **3:** 320, 1955.

[9] —, —, AND BLACKBURN, H. W.: The effect of leads utilized upon discrepancies between spatial vectors recorded by SVEC and by mean vector methods. Circulation Research **3:** 152, 1955.

[10] KATZ, L. N.: Significance of T wave in electrogram and electrocardiogram. Physiol. Rev. **8:** 447, 1928.

[11] SIMONSON, E., SCHMITT, O. H., DAHL, J., FRY, D., AND BAKKEN, E. E.: The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart. Am. Heart J. **47:** 122, 1954.

[12] —: The electrocardiogram in coronary heart disease. Minnesota Med. **38:** 871, 1955.

Bergy, G. G., and Bruce, R. A.: Discrepancies between Subjective and Objective Responses to Mitral Commissurotomy. New England J. Med. **253:** 887 (Nov. 24), 1955.

Thirty-one patients were re-evaluated an average of 21 months following mitral commissurotomy for mitral stenosis. The usual methods of evaluation were used and, in addition, a standard exercise test that required the patient to walk for 10 minutes at 1.73 mph on a 10 per cent grade. A physical fitness index of over-all cardiorespiratory performance was determined from observations made during this test.

In reply to a questionnaire, 29 of 31 patients classified themselves as better and 7 reported relapses due to heart failure or manifestations of the postcommissurotomy syndrome. Twenty of the patients, have some persistent limitation, 15 required daytime periods of rest, and all but 4 still required some form of medication. The most common limiting symptom was exertional dyspnea for 19 patients and ease of fatigue for 15 patients. Prior to operation 17 of the 31 patients could do full-time work, but all but 3 of them had some limitation with exertion; following operation 24 patients could work full time, and 15 instead of 3 had no limitations with effort. Prior to the operation 11 patients were totally disabled; this was the case in only 3 following surgery. Following surgery the murmur of mitral stenosis never disappeared although it was often less intense. The frequency of mitral insufficiency as determined by auscultation increased from 13 to 15 patients after surgery whereas atrial fibrillation decreased from 16 to 11 patients.

Exercise tolerance tests were possible in 29 patients. Following operation 26 were able to walk 10 minutes in contrast to 21 preoperatively, normal respiratory efficiency was achieved by 10 in contrast with 7 prior to surgery, and a normal physical fitness index score was made by 15 patients as compared with 9 previously.

There was correlation of subjective improvement with objective evidence in only 55 per cent of the patients. The authors express the belief that for some patients the term "better" describes a change in attitude toward their disease and disability, rather than improvement in cardiorespiratory function. This change in attitude may result from many factors including the positive, enthusiastic approach of the surgeon and careful medical supervision. The increase in the mean physical fitness index in the group of patients reported here was hardly greater than that in a similar group of patients studied in the same laboratory and treated only by medical therapy. The problem of differentiating patients with myocardial insufficiency from those with mechanical block at the mitral valve makes evaluation of response to treatment difficult.

ROSENBAUM

Studies on the Control of Hypertension. VII. Effects of Ganglionic Blockade Combined With Hydralazine on the Malignant Stage Complicated by Renal Azotemia

By H. Mitchell Perry, Jr., M.D., and Henry A. Schroeder, M.D.

The malignant stage of arterial hypertension complicated by azotemia is usually a rapidly fatal disorder. The elevated blood pressures of 82 patients in this stage were chronically lowered by the regular, continued use of oral ganglionic-blocking agents and hydralazine hydrochloride in doses sufficient to control their hypertension without provoking dangerous hypotension or further azotemia. By careful administration of these potent antihypertensive drugs the mortality rate of azotemic patients was significantly reduced. The malignant stage of hypertension that has progressed to moderate renal insufficiency is no longer a rapidly fatal disease when properly treated, while that which has progressed further is usually uninfluenced.

THE oral administration of frequent variable doses of an autonomic-blocking agent and hydralazine has been shown to lower the blood pressure of hypertensive patients as long as the drugs were given.[1-3] Moreover, their use has been accompanied by an increased period of survival for patients with malignant stages of hypertension[4] as compared to untreated patients with similarly severe disease.[5-7] The toxicities of both types of drugs have been discussed together in general terms[8] and separately in more detail.[9, 10] In an attempt to define the limitations of treatment, data are presented for all of our patients who had malignant stages of hypertension that had progressed to the point of nitrogen retention before the inception of drug therapy. The initial severity of the disease, the antihypertensive regimen, the changes following therapy, the period of survival, and the cause of death have been tabulated.

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, Saint Louis, Mo.

This work was supported by a grant-in-aid from the National Heart Institute, U. S. Public Health Service, Lasdon Foundation, Ciba Pharmaceutical Products, Inc. and Burroughs Wellcome & Company, Inc.

Methods

Of the patients admitted to Barnes Hospital between August 1, 1951, and August 1, 1955, with malignant stages of hypertension and renal azotemia, 82 were treated with a combination of ganglionic blockade and oral hydralazine under the direct supervision of one of the authors. In this paper *malignant stages of hypertension*, or more simply *malignant hypertension*, is a clinical diagnosis that makes no prediction about the presence of renal arteriolar necrosis. As used here *malignant hypertension* is characterized by a persistent elevation of diastolic pressure at rest in the hospital above 120 mm. Hg, hemorrhagic and exudative retinitis with papilledema, proteinuria, and markedly diminished renal function. In addition, all the patients considered had nitrogen retention that failed to disappear after the correction of heart failure. Thirty-nine of the 82 patients* were female, 28 were Negro, and 45 were ward patients. Therapy was begun for 21 during the first year of the study, for 18 during the second, for 22 during the third, and for 21 during the fourth. On admission to the hospital 8 patients were believed to have hypertensive encephalopathy, manifested by confusion or coma; 7 others had pulmonary edema, and 12 more showed significant signs of left ventricular failure. Five patients had histories suggesting that they had suffered apoplectic strokes, and 2 had electrocardiographic evidence of previous myocardial infarction; 4 had had surgical sympathectomies.

* Some patients previously reported[4] are not included, since the authors did not actually supervise therapy although they were consulted.

Control data included each patient's mean pretreatment blood pressure, which was calculated by averaging all values determined by nurses at four hour intervals in the hospital with the patient in a supine position. The mean number of such determinations was 10, the maximum was 37, and, except in the case of the 15 acute emergencies, the minimum was 6. None of the 16 sodium amytal release tests that were performed produced diastolic normotension. In every case the ocular fundi were examined, and at least one hemogram and a pair of urinalyses were obtained. Except for the 7 patients who had pulmonary edema, the degree of azotemia was measured in the absence of evident cardiac failure and before antihypertensive therapy. Everyone with an initial level of nonprotein nitrogen below 31 mg./100 ml. plasma was excluded from the series, although 25 mg. is the upper limit of normal in the Barnes Hospital Laboratories; the unusually low values are due to precipitation of the protein by zinc hydroxide, which removes glutathione, ergothioneine, uric acid, and perhaps other substances that are not precipitated by the more usual phosphotungstic acid procedure.[11] In 67 patients renal function was measured by the urinary excretion of phenol red within 15 minutes of its intravenous injection. Cardiac status was evaluated by physical, electrocardiographic, and roentgenologic examination, as well as by symptomatology.

The method of administering a constant dose of hydralazine and a simultaneous, variable dose of autonomic-blocking agent depending on the systolic pressure of the seated patient has previously been reported.[3] All medication was oral except in an initial emergency situation. Every patient who went home was instructed to continue the antihypertensive regimen worked out for him in the hospital. In only 1 case did this include salt restriction, and in only 6 was digitalis prescribed. Each patient was given a sphygmomanometer and adequate instructions in its use. The follow-up data involving blood pressure and medication were determined on readmission to the hospital, by careful interrogation on return visits, and from the continuous charts that each patient was requested to fill out daily and hand in at regular intervals. During treatment the blood pressure was ordinarily taken five times a day with the subject in a sitting posture in order to gage the required amount of autonomic blocking agent; hence the weekly pressure and dosage for each individual patient were the averages of approximately 35 recordings. For purposes of simplicity these individual means were frequently further consolidated into group means. At intervals reexaminations were made by the original physician and in the same laboratories to reevaluate cardiac and renal status as well as the general condition of the patient. Close questioning of each individual about his activities permitted a subjective estimate of rehabilitation. A continuing effort was made to follow all patients, and whenever possible survival time and cause of death were ascertained. The study was closed in August 1955.*

Results

Of the 82 patients with malignant hypertension and pretreatment renal azotemia, 66 continued therapy. Of these, 28 are alive after an average of 21.4 months and 38 died after an average of 4.7 months. The 66 were arbitrarily divided on the basis of the extent of nitrogen retention before treatment. Twenty-seven of the 46 patients with less than 61 mg. nonprotein nitrogen per 100 ml. of plasma are being successfully maintained on therapy; whereas only 1 of 20 patients with more marked azotemia has survived. Table 1 indicates survival time as a function of pretreatment azotemia. Figure 1 indicates the length of time that each living patient has followed an antihypertensive regimen. Figure 2 presents similar data for patients who have died.

The remaining 16 patients discontinued therapy; all had less than 61 mg. nonprotein nitrogen per 100 ml. of plasma before treatment. Four, including 2 private patients, were lost to follow-up immediately after discharge from the hospital and presumably are dead. The other 12 are known to have died within a month of discontinuing antihypertensive drugs. Eight of these died with uremia less than 60 days after starting therapy, half in 1951 and half

* Slow increases in nitrogen retention that were persistent and significant have only been observed in case 1, and in 2 other patients of our series of over 500 under treatment. A 34-year-old man with probable chronic glomerulonephritis and formerly in the malignant stage of hypertension was normotensive under therapy for 30 months until he developed a severe upper respiratory infection in November 1955 after this study was closed. Subsequently his nonprotein nitrogen, which had remained between 50 and 70 mg./100 ml. blood, increased to 118 mg. in April 1956. He is normotensive and working at the time of writing. A 52-year-old malignant hypertensive woman, who was not included in the study because she was not azotemic when first treated in October 1951, developed slowly progressive nitrogen retention after 40 months of therapy and died with uremia in March 1956. Chronic pyelonephritis was found at autopsy. In these 2 cases the underlying renal diseases not dependent upon nephrosclerosis were unaffected by control of blood pressure.

TABLE 1.—*Mortality as a Function of Nitrogen Retention in 66 Patients Who Continued Therapy*

Pretreatment Nonprotein Nitrogen mg. %	No. of Patients	Av. No. of Months Lived	Mortality Per cent	Surviving Patients		Deceased Patients	
				No.	Av. No. of Months Lived	No.	Av. No. of Months Lived
30–39	31	19.3	42	18	28.1	13*	7.0
40–49	10	4.1	50	5	2.2	5	5.9
50–59	5	14.4	20	4	17.6	1	1.5
Subtotal	46	15.5	41	27	21.8	19*	6.4
60–79	12	3.7	92	1	11.0	11	3.3
80–99	1	0.5	100	—	—	1	0.5
⩾100	7	2.7	100	—	—	7	2.7
Subtotal	20	3.3	95	1	11.0	19	2.8
Total	66	11.6	58	28	21.4	38*	4.6

* 8 died with fibrinous pneumonitis in the absence of uremia.

since; in each instance therapy was stopped after a marked increase in nitrogen retention coupled with complete prostration and often with confusion. The remaining 4, including 2 private patients, died 3, 6, 9, and 15 months after treatment was begun: the first following an episode of hypertensive encephalopathy; the second and third after cerebral hemorrhage, and the last as a result of progressive malignant hypertension when hydralazine was discontinued because of disseminated lupus erythematosus.

During the inception of therapy, azotemia increased in the surviving patients by an average of 18 mg. nonprotein nitrogen per 100 ml. of plasma, with the maximum rise being 54 mg.; however, by the time of their discharge from the hospital the mean level was 6 mg. below its original value. Figure 3 indicates the relationship of blood pressure, medication, and azotemia (as blood urea nitrogen) during the initial hospitalization of an 18-year-old white man with acute malignant hypertension and polycystic kidneys. The patient, who has continued almost normotensive on medication, is asymptomatic and working full-time; he is not included in the series because he was treated at another hospital. Figure 4 gives similar data for an older Negro man who also had malignant hypertension and pretreatment

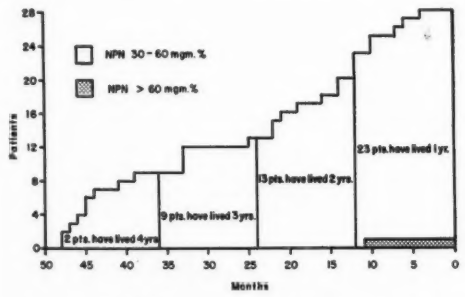

NPN 30-60 mgm.%
NPN > 60 mgm.%
Patients
Months
2 pts. have lived 4 yrs.
9 pts. have lived 3 yrs.
13 pts. have lived 2 yrs.
23 pts. have lived 1 yr.

FIG. 1. Post-treatment survival time of 28 living patients who had malignant hypertension. The open bars indicate patients who had 30 to 60 mg. nonprotein nitrogen/100 ml. plasma before antihypertensive therapy. The cross-hatched bar indicates the patient with 64 mg. nonprotein nitrogen/100 ml. plasma before therapy.

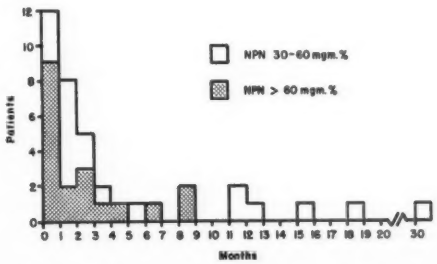


FIG. 2. Post-treatment survival time of 38 deceased patients who had malignant hypertension and who continued therapy. The open bars indicate patients who had 30 to 60 mg. nonprotein nitrogen/100 ml. plasma before antihypertensive therapy. The cross-hatched bars indicate those with greater degrees of nitrogen retention before therapy. Of the 13 patients in the former group who died within six months of instituting therapy, 7 had the marked tachypnea and anatomic lesions of fibrinous pneumonitis.

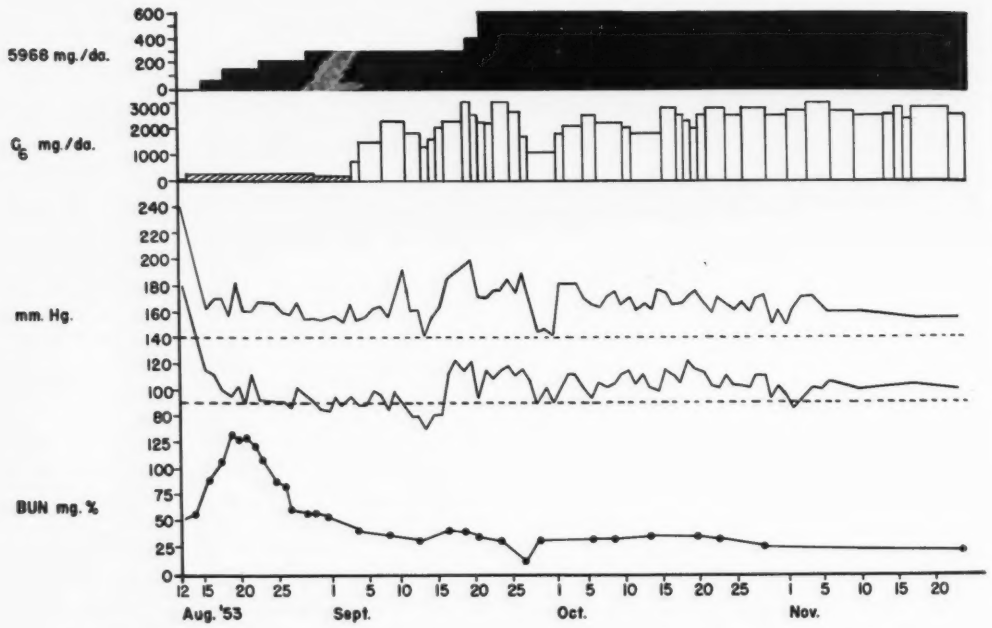


FIG. 3. Medication, blood pressure, and nitrogen retention during hospitalization. The solid bars represent oral hydralazine (5968). The cross-hatched bars represent parenteral, and the open bars oral hexamethonium chloride (C_6). The parenteral dose has been multiplied by 10 in order partially to compensate for the much greater efficacy of this route of administration. Each of the points on the blood pressure curve is the average of at least six, and initially as many as 24, determinations. All were made with the patient supine. Note that azotemia is shown in terms of blood urea nitrogen rather than total nonprotein nitrogen.

Except for life-long enuresis, this 18 year old white man was entirely well until three days before he entered the hospital. Pyrexia and malaise were followed by lethargy, emesis, disorientation, and coma. Physical examination revealed papilledema, hemorrhagic retinitis, minimal cardiomegaly, and a presystolic gallop. Roentgenologic examination suggested polycystic kidneys, and 3 plus albuminuria was found. After returning home the patient did very well. He was working when last seen in July 1955, when physical examination, including funduscopic examination, was normal. His urine contained no protein. His antihypertensive regimen called for a maximum dose of 750 mg. of oral hexamethonium chloride and a constant dose of 100 mg. of hydralazine every four hours. His sitting blood pressure at home averaged 160/80 mm. Hg.

azotemia. He is not inluded in the serices either, because he was discharged from the hospital too recently. Another example of the reciprocal relationship between hypertension and nitrogen retention has been published.[4]

Table 2 indicates the blood pressure before and after therapy as well as the amount of drug necessary to maintain the antihypertensive effect for the 28 living patients who had malignant hypertension and pretreatment azotemia. The values one month after discharge from the hospital are included for comparison with those occurring at yearly intervals. The pretreatment blood pressure is a measure of the severity of the hypertensive process, and the post-treatment levels indicate how well the original control of blood pressure has been maintained. In terms of hexamethonium chloride* the azotemic patients

* Except for brief transition periods two or more autonomic blocking agents were not simultaneously administered. Fifty-six patients received only hexamethonium chloride, 15 both hexamethonium chloride and pentolinium tartrate, 7 only pentolinium tartrate, 3 both hexamethonium chloride and 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline dimethochloride (Ecolid, Ciba Su-3088), and 1 all 3 ions. All dosages cited are in terms of oral hexa-

ngested an average of 2.42 Gm. of ganglionic-blocking agent per day after a month at home. The decreased requirement of the drug at two years is not real, since the 13 patients who have been treated that long were initially ingesting an average of 1.86 Gm. of hexamethonium chloride a day. Although the mean daily intake of oral hydralazine exceeded 0.5 Gm. for a considerable period in many, only 4 patients developed any signs of hydralazine toxicity.†

Table 2 also lists laboratory data for the 28 living patients. The disappearance of hemorrhages and exudates from the ocular fundus may indicate a generally improved condition of the small afferent vessels. The diminished albuminuria contrasts with the persistent azotemia and the continued inability to concentrate urine or excrete phenol red. Although cardiomegaly was absent roentgenologically and electrocardiographically in only 2 after a year of therapy, the status of the heart appeared objectively improved in most instances. There was no significant change in the mild anemia during three years of treatment.

Few patients were doing any work before therapy or within a month of hospital discharge. By the end of the first year of treatment, however, most of the survivors had returned to some job. After two and three years the percentage of those gainfully employed had increased (table 2). Several have

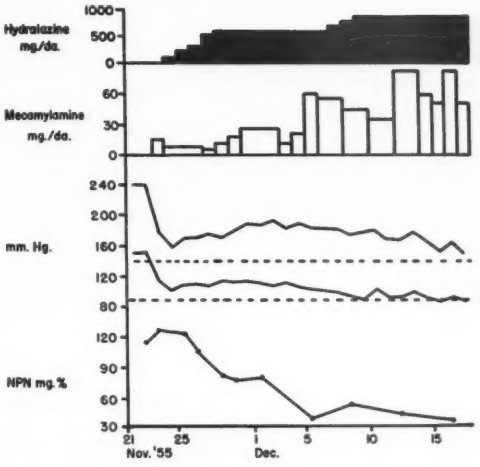


FIG. 4. Medication, blood pressure, and nitrogen retention during hospitalization. The solid bars represent oral hydralazine. The open bars represent oral mecamylamine (Inversine, Sharpe & Dohme). Each of the points on blood pressure curve is the average of at least six, and initially as many as 24, determinations. All were made with the patient supine. In addition to the medication shown, 513 mg. of intramuscular hexamethonium chloride were administered on November 22 without any effect on the blood pressure.

Except for probable pyelonephritis 10 years previously, followed by the discovery of high blood pressure, this 45 year old Negro policeman was essentially asymptomatic until six months before he entered Barnes Hospital. Progressive asthenia and increasingly frequent periods of syncope associated with vertigo and amblyopia were followed by urinary frequency and dyspnea, and finally nausea and vomiting. There was hemorrhagic retinitis with bilateral papilledema. Cardiomegaly was present, the lung fields were clear to percussion and auscultation, and there was no edema. There were cylindruria and 3 plus albuminuria; 100 ml. of blood contained 10 Gm. of hemoglobin. Electrocardiograms and roentgenograms of the chest indicated left ventricular enlargement. Azotemia and blood pressure decreased following the institution of oral mecamylamine and hydralazine therapy. The patient was discharged from the hospital with a regular diet without digitalis. He had no symptoms except amblyopia referable to his hypertension or to his therapy, and he returned to work three weeks later. There were 67 mg. nonprotein nitrogen/100 ml. plasma on January 20, 1956, and 71 mg. on February 24, 1956.

been able to resume moderately hard manual labor such as farming or truck driving; whereas others, like the subject of the second case report, have adopted less strenuous occupa-

methonium chloride. When necessary the dose of oral pentolinium tartrate has been multiplied by 5 in order to render it comparable.[12]

† Among the 28 patients who survived a year of therapy, 4 who had achieved good control of their blood pressures had manifestations of delayed hydralazine toxicity. Two white women developed arthritides, an increased cephalin-cholesterol flocculation of their serum, and circulating lupus erythematosus cells. A Negro woman with clinical findings characteristic of infectious hepatitis was found to have many lupus erythematosus cells in her peripheral blood. She is one of the 16 patients listed as having discontinued therapy, although she discontinued only hydralazine. Despite 1 gram of oral Ecolid daily her diastolic pressure averaged more than 160 mm. Hg in the sitting position during the six months before she died of progressive malignant hypertension terminating in renal failure. Another Negro woman, whose case is reported in detail as an example of "fibrinous pneumonitis" resulting from ganglionic-blocking agent,[10] was suspected of showing toxicity to hydralazine as well.

TABLE 2.—*Blood Pressure, Dosage, and Laboratory Data in 28 Surviving Patients with Malignant Hypertension and Pretreatment Azotemia*

	Before therapy	1 month*	1 year*	2 years*	3 years
Number of patients	28	28	23	13	9
Systolic pressure, mm. Hg	223	160	162	161	162
Diastolic pressure, mm. Hg	142	99	102	99	98
Blocking agent,† Gm./day orally	0	2.42	2.50	1.94	1.93
Hydralazine, Gm./day orally	0	0.54	0.51	0.34	0.31
Hemorrhagic and exudative retinitis with papilledema	100	—	0§	0	0
Albuminuria, graded 0 to 4+	2.5	—	1.0	0.9	0.9
Nonprotein nitrogen, mg. %	39	40	38	41	47
Maximum urinary specific gravity	1.013	—	1.015	1.012	1.01
Phenolsulfonphthalein, % excreted in 15 minutes	7	—	10	6	13
Cardiomegaly by x-ray, % improved	93‡	—	52	62	78
Electrocardiographic abnormalities, % improved	100‡	—	57	54	67
Hemoglobin, Gm. per 100 ml.	12.5	—	11.9	12.1	11.6
Working, %	8	5	68	78	91

* After discharge from the hospital
† Calculated as oral hexamethonium
‡ Per cent with abnormalities
§ 6 patients exhibited hard exudates without hemorrhages or papilledema

TABLE 3.—*Postmortem Findings in 32 Patients*

	Pretreatment Nonprotein Nitrogen mg. %	Total No.	No. Dead	No. of Autopsies	Fibrinous pneumonitis	Cerebral vascular accident	Mycoardial infarction	Cardiac failure	Pyelonephritis	Renal failure (terminal NPN > 100 mg. %)	Renal arteriolar necrosis
Patients who continued treatment	31–60	46	19	11	9	1	0	2	1	1	3
Patients who continued treatment	61–137	20	19	13	6	0	0	7	2	13	4
Patients who discontinued treatment	31–60	16	12	8	3	0	1	6	1	7	6
Total		82	50	32	18	1	1	15	4	21	13

tions. The 9 patients treated three years initially had severe symptoms of autonomic blockade; however, all were doing some work within a year of discharge from the hospital and now none has symptoms referable to his drugs.

Of the 50 patients known to be dead, autopsies were performed in 32 of the 34 who died in the hospital. Some postmortem findings are summarized in table 3. Fibrinous pneumonitis[10] was found anatomically in 9 of 11 patients without excessive pretreatment azotemia who continued their therapy. Of these only 1 had renal failure (case report 1); whereas 8 died with less than 60 mg. nonprotein nitrogen per 100 ml. of plasma, with the terminal tachypnea that has been associated with large doses of ganglionic blocking agents, and with no other obvious reason for demise. Six of the 8 died during 1951 and 1952. One of the 2 patients without fibrinous pneumonitis died of an apoplectic stroke and the other with heart failure.

Among the patients who discontinued

herapy and among those who initially had ore than 60 mg. nonprotein nitrogen per 100 l. of plasma, renal and cardiac failures were he rule; moreover fibrinous pneumonitis was ot found without uremia. In the entire 32 utopsies significant pyelonephritis was found nly 4 times; recent myocardial infarction and erebral vascular accident were each discovered nce. Renal arteriolar necrosis was most ommon in the group with the greatest pre-reatment nitrogen retention; however, it was resent in 3 of 11 patients who had less than 0 mg. nonprotein nitrogen at the time of eath.

Two illustrative cases, one of a living and one of an expired patient, are reported accompanied by graphs indicating medication, mean blood pressure, and azotemia before and during treatment.

Reports of Cases

Case 1. This 40 year old white man was first admitted to Barnes Hospital in February 1952 with paroxysmal frontal headaches that had begun two years previously. These increased in severity and became associated with emesis and syncope, making the patient permanently bedfast nine months prior to hospitalization. Systolic pressure varying between 180 to 240 mm. Hg and 4 plus albuminuria were present during this period. In the two months immediately before he entered the hospital, he lost 11 Kg. of weight; in addition amaurosis, asthenia, and hematuria appeared. There was no history suggestive of renal or cardiac failure.

Except for a supine blood pressure of 286/180 mm. Hg, his vital signs were within normal limits when he was admitted to the hospital. He was asthenic but alert and cooperative. There was papilledema as well as hemorrhagic and exudative retinitis. The lungs were clear to percussion and auscultation. Cardiomegaly and an apical systolic gallop were present. No peripheral edema nor abnormal abdominal findings were noted. There were 14.0 Gm. hemoglobin per 100 ml. blood; urinalyses revealed 3 plus albuminuria, cylindruria, and microscopic hematuria. The determination of fecal blood by guaiac was 3 plus. There were 38 mg. nonprotein nitrogen per 100 ml. plasma. Less than 8 per cent of intravenously injected phenol red was excreted in 120 minutes. Urine cultures were repeatedly negative. The circulating electrolytes were within normal limits. Electrocardiograms and roentgenograms of the chest revealed cardiomegaly. Roentgenologic air-contrast studies made in search of a pheochromocytoma revealed only bilaterally small kidneys. Neither benzodioxane nor sodium amytal lowered the diastolic blood pressure below 180 mm. Hg.

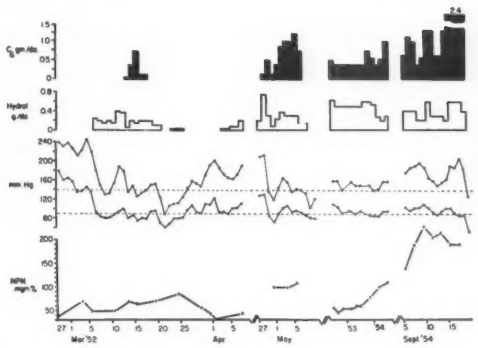


Fig. 5. *Case 1.* Oral medication, blood pressure, and azotemia are indicated during both hospitalizations and the intervening period. Twenty uneventful days during the first hospitalization have been omitted and the time scale for the interval between hospitalizations has been shortened. At the extreme right the daily dose of hexamethonium chloride is indicated by the broken bar to be 2.4 Gm. The figures for blood pressure and medication at home are bimonthly averages; in the hospital they are daily averages and represent 6 to 24 recorded values. All blood pressures were taken with the patient in a sitting position.

As shown in figure 5 the blood pressure was initially lowered with oral hexamethonium chloride. When tolerance appeared within a few days, it was quickly overcome by the addition of hydralazine; however, with normotension disorientation had appeared and only gradually resolved. During a stormy 10 weeks in the hospital ganglionic blockade produced urinary retention and the resultant catheterization led to infection of the genitourinary tract with a strain of *Escherichia coli* that proved resistant to all available antibiotics. His nonprotein nitrogen level increased to 108 mg./100 ml. of plasma. Two months after the patient had returned home, taking 500 mg. of hydralazine and 375 mg. of hexamethonium chloride a day, he had regained his mental facilities and 15 Kg. of weight; moreover there were only 48 mg. nonprotein nitrogen per 100 ml. plasma. Slowly both his strength and his azotemia increased, but his nutritional and mental status remained unaltered, and his blood pressure was unchanged.

In May 1954, he first began to complain of vague abdominal pain. At this time 1 plus albuminuria was found without other urinary abnormalities. There were 6300 leukocytes per cu. mm. blood, 10.5 Gm. hemoglobin/100 ml. blood, and 110 mg. nonprotein nitrogen, 84 mg. cholesterol, 5.6 Gm. albumin, and 1.9 Gm. globulin/100 ml. plasma. No circulating lupus erythematosus cells were seen, and the sedi-

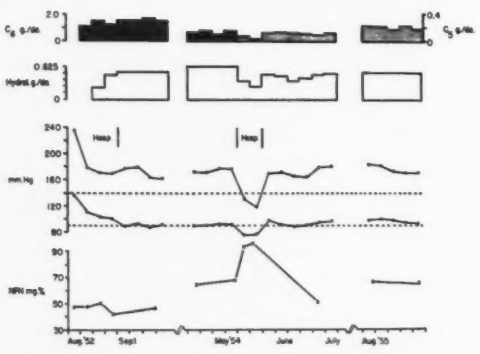


FIG. 6. *Case 2.* Medication, blood pressure, and azotemia are indicated on the same time axis for three different periods. The figures for blood pressure and medication are weekly averages and represent 35 recorded values at home and 42 in the hospital; the pressure readings were taken with the patient in a sitting position. The oral dosage of hexamethonium chloride is represented by solid bars and that of pentolinium tartrate by cross-hatched ones.

mentation rate was 1 ml./hr. In August, increasing diarrhea and emesis began, and he was readmitted to Barnes Hospital after 28 months at home because of an acute episode of gastrointestinal bleeding. He appeared chronically ill but his vital signs were within normal limits except for a blood pressure of 200/100 mm. Hg. Funduscopic examination revealed no hemorrhages, exudates, or papilledema. Many fine crackling rales were heard at the bases of both lungs posteriorly, cardiomegaly was more pronounced than previously, and there was bilateral ankle edema. There were 6.9 Gm. hemoglobin/100 ml. blood. Urinalysis revealed 2 plus albuminuria and microscopic hematuria without cylindruria. The determination of fecal blood by guaiac was 4 plus. There were 140 mg. nonprotein nitrogen, 14.4 mEq sodium, 2.07 mEq carbon dioxide, 4.3 Gm. albumin, and 1.5 Gm. globulin/100 ml. plasma. The electrocardiogram revealed left ventricular enlargement on the basis of voltage alone. Cephalin-cholesterol flocculation of the serum was 4 plus and thymol turbidity 0.5 units. Although transfusions with packed red blood cells almost doubled his circulating hemoglobin concentration, the level of nonprotein nitrogen in the plasma rose abruptly to 240 mg./100 ml. and never again fell below 200 mg. On the sixteenth hospital day, death resulted from pulmonary edema.

At autopsy the body weighed 49 Kg. and the heart 490 Gm. Together the kidneys weighed 105 Gm. and the lungs 1800 Gm. There was advanced arteriolar nephrosclerosis without necrosis. Every glomerulus appeared diseased; many were fibrotic, and frequently the basement membrane of the capillary tuft was greatly thickened by an almost homogeneous, eosinophilic material. There were also cardiac hypertrophy and mucosal ecchymoses in the rectosigmoid colon. Pulmonary congestion and fibrinous pneumonitis[10] were prominent. In some areas of the lung there was dense homogeneous material in the alveolar spaces that stained deeply with eosin and resembled a hyaline membrane; into it infrequent fibroblasts were growing; intra-alveolar hemorrhage associated with focal necrosis was present.

Case 2. This 49 year old white man was operating his own steam shovel until he first entered Barnes Hospital in August 1952, with a history of hypertension for 11 years. His initial symptom was a "slight stroke" without residual six weeks before admission. The only other complaints were amblyopia and nocturia, which appeared soon thereafter. In the hospital his blood pressure was 215/140 mm. Hg; temperature, pulse, and respirations were normal. Hemorrhagic and exudative retinitis associated with papilledema was seen. Save for cardiomegaly the rest of the physical examination was normal. There was 3 plus albuminuria; 13.2 Gm. hemoglobin/100 ml. blood and 48 mg. nonprotein nitrogen/100 ml. plasma were present. Only 2 per cent of intravenously injected phenol red was excreted within 15 minutes. Both electrocardiogram and roentgenogram of the chest indicated left ventricular enlargement. Other laboratory studies were not remarkable. Oral hexamethonium chloride and hydralazine were instituted according to the previously described regimen[3] with minimal side effects. After a month he went home with the medications and blood pressure indicated in figure 6.

He reentered Barnes Hospital 45 days later because of dysuria, anorexia, weight loss, and intermittent diarrhea and constipation without nausea or vomiting. His blood pressure was 160/90 mm. Hg; "hard" exudates but neither papilledema nor hemorrhages were observed in the ocular fundi; otherwise the physical signs were unchanged. There was 1 plus albuminuria and 40 mg. nonprotein nitrogen/100 ml. plasma. Since considerable infected residual urine was found, transurethral prostatectomy was performed, following which the nonprotein nitrogen rose to 82 mg./100 ml. plasma. After six weeks of supportive therapy the azotemia returned to its previous level, and he returned home with little improvement in his gastrointestinal symptoms. Six months later these had diminished considerably and he had returned to full-time office work.

Azotemia, blood pressure, and intake of antihypertensive agents during the fourth admission to Barnes Hospital in May 1954 are indicated in figure 6. He reentered because of continuing minimal anorexia and constipation. The blood pressure was 170/100 mm. Hg. Funduscopic examination revealed no hemorrhages, exudates, or papilledema. The lungs were clear, and the heart did not seem to be enlarged; the liver was felt 3 cm. below the costal margin, but peripheral edema was not found. There were 12 Gm.

emoglobin/100 ml. blood and 8000 leukocytes per
1. mm. blood. A trace of albuminuria persisted and
any leukocytes were found in the urine. There were
2 mg. nonprotein nitrogen/100 ml. plasma, but
ne concentrations of circulating proteins were
ormal. Cephalin-cholesterol flocculation and thymol
rbidity of the serum were within normal limits, and
o lupus erythematosus cells were seen in peripheral
lood. The electrocardiogram was markedly im-
roved in comparison to the original record, and the
hest film substantiated the decrease in cardiac size.
When the autonomic-blocking agent was changed
rom hexamethonium to pentolinium ion, the blood
ressure fell to unusually low levels and the non-
protein nitrogen immediately rose to 94 mg./100 ml.
plasma. Despite this he was sent home, where his
blood pressure returned to its usual level and his
nitrogen retention decreased.

Another prostatectomy was performed in Febru-
ary 1955, following intermittent bouts of pyuria and
the discovery of 200 ml. of residual, infected urine.
At this time his blood pressure was 155/95 mm. Hg.
The physical examination was unchanged. There
were 11 Gm. hemoglobin/100 ml. blood. A trace of
albumin persisted. There were 69 mg. nonprotein
nitrogen/100 ml. plasma; this value rose to 85 mg.
following surgery but fell to 61 mg. before discharge.
Since discharge he has had no further complaints,
and he continues to work a full day running his own
construction business.

Discussion

The patients considered here were all in the final stages of a rapidly progressive fatal disease. With antihypertensive regimens, some have lived and worked for years. The 12 patients who are known to have died within a month of discontinuing therapy indicate the severity of the disease. The fact that only 8 discontinued therapy without our consent is a measure of how well patients accepted such a regimen. Cardiac status gradually improved with tension sustained near normal but renal function changed little. In consideration of the prognosis without treatment, the hazards of therapy are slight. The danger of acute renal failure following relative hypotension can be largely obviated by carefully titrating blood pressure against nitrogen retention. Delayed toxicity to hydralazine, which may simulate disseminated lupus erythematosus, vanished upon cessation of the offending drug. Reactions to ganglionic blockade, although less readily reversible, have become increasingly rare as the drugs are more effectively used.

Summary

A combination of ganglionic blocking agent and 1-hydrazinophthalazine was given orally to 82 patients with malignant hypertension and nitrogen retention. Of 46 who had between 30 and 60 mg. nonprotein nitrogen per 100 ml. plasma and who continued on adequate therapy, 27 are alive and working after an average of 21.8 months; almost half have been treated for two years. Only one of 20 patients with more severe initial azotemia is living. The survivors have maintained near normotension; for them cardiac function has improved, but renal function has not changed. Heart failure occurred 15 times and kidney failure 21 times in the 32 autopsied patients. The major post-mortem diagnoses were fibrinous pneumonitis in 18, renal arteriolar necrosis in 13, pyelonephritis in 4 and myocardial infarction and cerebral vascular accident in one each; however, in the 11 cooperative patients with initially mild azotemia, uremia occurred only once and fibrinous pneumonitis eight times.

Summario in Interlingua

Le combination de un agente ganglioblocante con 1-hydrazinophthalazina esseva administrate oralmente a 82 patientes con hypertension maligne e retention de nitrogeno. Inter le 46 patientes, qui habeva inter 30 e 60 mg nitrogeno nonproteinic per 100 ml plasma e qui continuava reciper un adequate therapia, 27 vive e labora post un intervallo median de 21,8 menses; quasi 50 pro cento ha essite sub tractamento durante duo annos. Un sol patiente ex le gruppo de 20 subjectos con plus sever azotemia initial es ancora inter le viventes. Le superviventes ha mantenite un tension quasi normal. In illes le function cardiac se ha meliorate, sed le function renal ha remanite inalterate. Disfallimento cardiac occurreva 15 vices e disfallimento renal 21 vices in le 32 patientes autopsiate. Le principal diagnoses post morte esseva pneumonitis fibrinose (18 casos), necrosis reno-arteriolar (14), pyelonephritis (4), infarcimento myocardial (1), e accidente cerebro-vascular (1). Tamen, in le 11 patientes cooperative con initialmente leve grados de azotemia, uremia

occurreva solmente un vice e pneumonitis fibrinose 8 vices.

REFERENCES

[1] SCHROEDER, H. A.: The effect of 1-hydrazinophthalazine and hexamethonium on hypertension. J. Lab. & Clin. Med. **38:** 949, 1951.

[2] —: Control of hypertension by hexamethonium and 1-hydrazinophthalazine. Preliminary observations. Arch. Int. Med. **89:** 523, 1952.

[3] —, MORROW, J. D., AND PERRY, H. M., JR.: Studies on the control of hypertension by Hyphex. I. Effect on blood pressure. Circulation **8:** 672, 1953.

[4] —, —, AND —: Studies on the control of hypertension by Hyphex. V. Effects on the course of the malignant stage. Circulation **10:** 321, 1954.

[5] WAGENER, H. P., AND KEITH, N. M.: Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine **18:** 317, 1939.

[6] SMITHWICK, R. H.: The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease. *In:* Hypertension, A Symposium. Minneapolis, University of Minnesota Press, 1951.

[7] SCHOTTSTAEDT, M. F., AND SOKOLOW, M.: The natural history and course of hypertension with papilledema (malignant hypertension). Am. Heart J. **45:** 331, 1953.

[8] MORROW, J. D., SCHROEDER, H. A., AND PERRY, H. M., JR.: Studies on the control of hypertension by Hyphex. II. Toxic reactions and side effects. Circulation **8:** 829, 1953.

[9] PERRY, H. M., JR., AND SCHROEDER, H. A.: Syndrome simulating collagen disease caused by hydralazine (apresoline). J. A. M. A. **154:** 67, 1954.

[10] —, O'NEAL, R. M., AND THOMAS, W. A.: Pulmonary disease following chronic chemical ganglionic blockade: A clinical study and a pathological comparison with anatomically similar lesions accompanying uremia. Am. J. Med. In press.

[11] SOMOGYI, M.: Method for preparation of blood filtrates for determination of sugar. J. Biol. Chem. **86:** 655, 1930.

[12] PERRY, H. M., JR., AND SCHROEDER, H. A.: The use of pentolinium tartrate with and without hydralazine in the treatment of severe hypertension. New England J. Med. **252:** 1057, 1955.

Gallavardin, L., Finas, C., and Oelbrandt, L.: Atrio-Ventricular Block and Pregnancy. Observations on Two Cases with Fatal Outcome. Arch. mal coeur **48:** 768, 1955.

The first case, an apparently normal 28-year-old woman without previous complaints, developed numerous episodes of syncope during the third month of a second pregnancy. The electrocardiogram showed a wide QRS with a separate slow initial component as in the Wolff-Parkinson-White syndrome, but the P-R was never less than 0.12 sec. The episodes could not be influenced by atropine or ephedrine, but ceased as soon as complete A-V block with a typical left bundle-branch block pattern appeared. Death occurred suddenly during the eighth month of pregnancy In a second similar case, the syncope appeared during the fifth month of pregnancy, followed by normal delivery. It reappeared during the following year, especially in the premenstrual period, but disappeared as soon as complete A-V block set in. The ventricular complex at this time as well as previously, showed deeply inverted, pointed T waves in leads I, and V_1 to V_4. Death occurred suddenly. The relation of A-V block to pregnancy and menstruation in these cases is attributed to hormonal influences.

LEPESCHKIN

CLINICAL PROGRESS

Clinical Manifestations of the Unperforated Aortic Sinus Aneurysm

By ISRAEL STEINBERG, M.D., AND NATHANIEL FINBY, M.D.

ANEURYSMS of the aortic sinuses (of Valsalva) are rare and are either congenital or acquired. The acquired types are chiefly due to syphilis or bacterial endocarditis. The congenital aneurysms are thought to be due to a developmental defect in either the aorticopulmonary septum or the elastic tissue of the aortic sinuses.

Morgan Jones and Langley in 1949,[1] in a classic paper, reviewed the literature; they recorded 43 autopsied cases of aortic sinus aneurysms and added 4 new ones. Venning in 1951[2] reported 3 additional cases, and Falholt and Thompson in 1953[3] described a case of unruptured congenital right aortic sinus aneurysm diagnosed by retrograde aortography and increased the number of congenital sinus of Valsalva aneurysms to 34. In 1954, Besabe and associates[4] added a case of congenital aortic sinus aneurysm with rupture into the right atrium due to bacterial endocarditis, which also caused embolic gangrene of a foot.

Nineteen cases of syphilitic aneurysm of the aortic sinuses have been reported in the English literature since 1914; the antemortem diagnosis was made only once. However, the advent of contrast visualization of the aorta has made possible the recognition of aortic sinus aneurysms in 9 additional cases.[5]

In a 10-year period, during which over 2,500 patients were studied by intravenous angiocardiography, 19 cases of unruptured aortic sinus aneurysms have been diagnosed at this center. Seventeen cases have been reported previously and of these, 8 were congenital; 3, associated with coarctation of the aorta[6]; 1, with coarctation of the aorta and bacterial endocarditis[7]; 1 with pseudocoarctation of the aorta[8]; and 3 with arachnodactyly.[9] The 9 acquired cases were due to syphilis: of these, 6 were associated with aneurysms of the ascending aorta; while 3 had aortitis with localization of the aortic sinuses.[5]

The 19 cases of unperforated aortic sinus aneurysms observed by us form the basis of this report. Experience gained from their study indicates that there are significant clinical clues that should suggest the diagnosis. Confirmation may then be had by angiocardiography.

NORMAL ANATOMY OF THE AORTIC SINUSES

The aortic sinuses are 3 small dilatations in the wall of the aorta immediately above the aortic valves. Each sinus lies just above the attachment of an aortic cusp. The right and left coronary arteries usually originate within 2 of the aortic sinuses; however, they may emerge immediately distal to the aortic sinuses. The aortic sinuses and their corresponding aortic valves are named according to the source of the coronary arteries. Thus, the right and left coronary arteries emerge from the right and left aortic sinuses, respectively. The remaining aortic sinus usually lies posteriorly, does not contain a coronary artery and, according to the newest nomenclature, is designated the noncoronary sinus.[1]

The aortic sinuses are intracardiac and cannot be identified on conventional roentgenography. During angiocardiography they appear as small dilatations at the root of the aorta immediately above the aortic valves, and are best visualized in the left anterior oblique projection.[10] Inconstant filling of the coronary arteries during angiocardiography

From the Departments of Medicine and Radiology, The New York Hospital-Cornell Medical Center, New York, N. Y.

Aided by a grant from the Mallinckrodt Chemical Works.

does not allow complete identification of the sinuses. However, in the left anterior oblique view, the right coronary sinus is anterior and just behind the sternum. The aortic sinuses of Valsalva are in close relation to all the cardiac chambers, particularly the right atrium and ventricle. The superior vena cava and the pulmonary artery, the left ventricle and left atrium are adjacent.

Clinical Features of Unperforated Congenital Aortic Sinus Aneurysms

Age, Sex, and Race. The ages in 9 congenital unperforated aortic sinus aneurysm patients varied from 7 to 47 years. All but 2 were under 30 years; the older patients had associated arachnodactyly. Six were male and 3 were female. Only 1 was Negro.

Associated Anomalies. Four patients with aortic sinus aneurysms had the classical findings of coarctation of the aorta, i.e., hypertension of the upper extremities, rib notching, and absent or diminished blood pressures of the lower extremities.[6] One of the patients with coarctation of the aorta had subacute bacterial endocarditis and aortic regurgitation.[7] Three had the classical findings of arachnodactyly.[9] One patient had pseudocoarctation of the aorta[8]; and 1, the youngest, aged 7 years, also had congenital mitral and aortic stenosis with generalized hypertrophy and dilatation of the cardiac chambers.

Fig. 1. Aneurysm of the right coronary sinus and coarctation of the aorta. Left anterior oblique angiocardiogram of a 27-year-old woman demonstrates an enlarged left ventricle, a dilated ascending aorta with an aneurysm of the right coronary sinus (arrow), coarctation of the aorta (arrow), and enlarged brachiocephalic vessels with prominent collateral arteries. (Previously published,[7] reproduced with the permission of the New England Journal of Medicine.)

Symptoms. All the patients with coarctation of the aorta were symptomatic; however, the symptoms were not due to the aortic sinus aneurysm but to the associated aortic disease. Headache, dizziness, epistaxis, and Jacksonian epilepsy led to physical examination and the diagnosis of coarctation of the aorta in 3; fever and bouts of dyspnea resulted in the discovery of a complicated subacute bacterial endocarditis in the fourth patient.

Two of the patients with arachnodactyly were free of cardiovascular complaints; the third had sudden onset of chest pain at the age of 47 years, apparently due to the onset of aortic regurgitation and mild heart failure. The patient with pseudocoarctation complained of nervousness and backache, probably due to a neurotic disposition; while the ninth case, a 7-year-old child, was chronically ill with dyspnea and easy fatigability.

Murmurs. All patients with congenital aortic sinus aneurysms had heart murmurs. Common to all was a loud, rough (grade 2 to 4) systolic murmur at the apex of the heart, heard all over the precordium and especially to the left of the sternum.[7-9] In 3 instances, aortic valvular lesions were also present and produced diastolic and systolic murmurs at the base of the heart.[7, 9]

In the 4 patients with coarctation of the aorta, there were in addition, interscapular bruits due to arterial collaterals. Resection of the coarcted segment and re-anastomosis of the aorta completely relieved the hypertension and

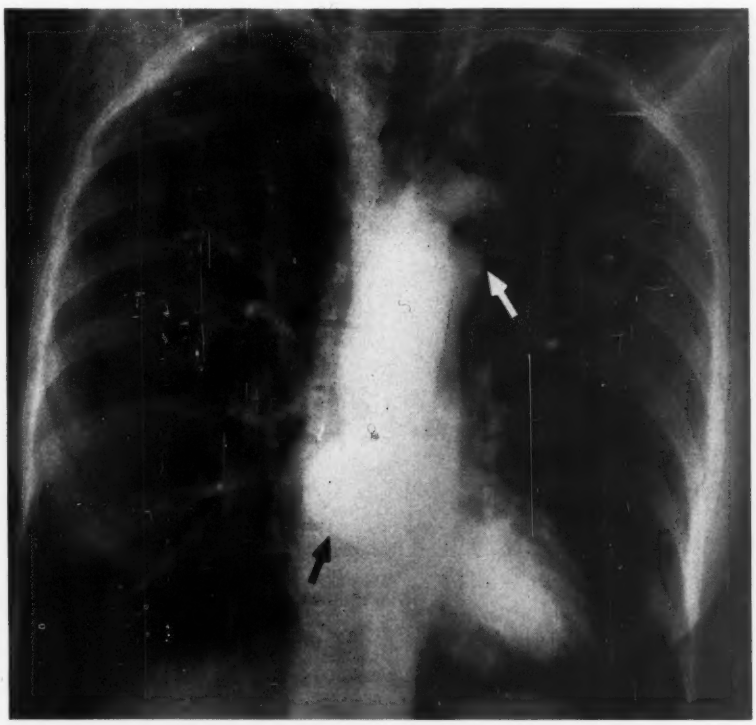


FIG. 2. Aneurysmal dilatation of the aortic sinuses and pseudocoarctation. Frontal angiocardiogram of a 26-year-old woman shows aneurysmal dilatation of the coronary sinuses (arrow) and pseudocoarctation of the aorta (arrow). Note the details of the pseudocoarctation and the dilated ascending and descending aorta. In addition to normal blood pressure readings in upper and lower extremities, direct readings of brachial and femoral arterial pressures showed no delay in blood flow, establishing the diagnosis of pseudocoarctation. (Previously published,[8] reproduced with the permission of the British Heart Journal.)

did away with the interscapular murmurs, but the cardiac murmurs were unaltered.

Blood Pressure. Systolic and diastolic hypertension was present in 3 of the patients with coarctation of the aorta; the fourth with aortic regurgitation had a systolic pressure of 190 mm. Hg but the diastolic blood pressure was 0. Two patients in this group had absent blood pressures in the legs and in 2, the lower extremity pressures were present but diminished. The patient with arachnodactyly and aortic regurgitation had an elevated pulse pressure, (140/60 mm. Hg); in the other 2 cases the blood pressure was normal.[9]

Electrocardiography. Left ventricular hypertrophy on electrocardiography was present in 2 of the 4 patients with coarctation of the aorta. Two others and the patient with pseudocoarctation had normal electrocardiograms. In the group with Marfan's syndrome, 1 had a normal electrocardiographic tracing, although conventional and angiocardiographic roentgenograms showed left ventricular hypertrophy; another had partial heart block with a normal-sized left ventricle; the third had left axis deviation and left ventricular hypertrophy.[9] The child with generalized cardiac chamber enlargements showed peak P waves indicative of atrial enlargement and inverted S-T and T waves suggestive of myocardial disease.

Roentgenography of Congenital Unperforated Aortic Sinus Aneurysms

Conventional Roentgenography. On fluoroscopy, unusual pulsation of the root and ascending aorta was frequent. However, the hypertension and dilated ascending aorta due to coarctation of the aorta and the aortic valve involvement in the majority of the cases limited the value of this observation.

An abnormal cardiac silhouette was present in all roentgenograms of patients with congenital aortic sinus aneurysms except in 1 instance; a patient with arachnodactyly had a normal heart. All cases with coarctation of the aorta, in addition, exhibited rib notchings and

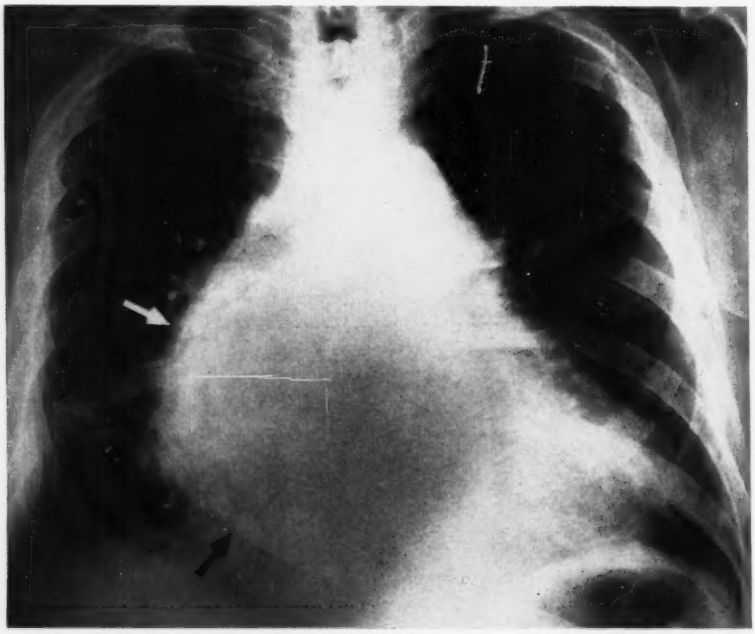


FIG. 3. Syphilitic aortitis with localized aneurysm of the aortic sinuses. Frontal roentgenogram of a 64-year-old man showing enlargement of the heart, pulmonary artery segment, and a massive calcified mass occupying most of the right upper cardiac silhouette (arrows).

n enlarged left ventricle. Evidence of post-tenotic enlargement of the descending aorta as seen and verified by indentation of the sophagus in 3 instances. The patient with seudocoarctation had a prominent shadow in he region of the aortic knob and a dilated lescending aorta; however, no rib notching was ecognized. Two of the patients with arach-odactyly had enlarged left ventricles. In the atient with aortic and mitral valve stenosis here was also enlargement of cardiac chambers.

Angiocardiography. Angiocardiography pro-vided the definitive diagnosis of aortic sinus aneurysm. Generalized aneurysmal dilatation of the aortic sinuses was present in all but 1 instance. In that case (fig. 1), only the right aortic sinus was involved. In the cases of co-arctation of the aorta, the point of coarctat on, the dilated brachiocephalic and collateral arterial branches as well as the enlarged left ventricle were clearly outlined (fig. 1). In contrast, in the case of pseudocoarctation (fig. 2), although there was an unusually dilated left subclavian artery, an apparent point of coarctation, and a dilated descending aorta, there was no collateral arterial circulation.

In *summary*, the only clue to the presence of an unperforated congenital aortic sinus aneurysm is a grade 3 to 4 systolic murmur over the heart, especially to the left of the sternum. Such a murmur if associated with coarctation of the aorta, anomalies of the aortic valves or arch, or arachnodactyly should arouse suspicion of an aortic sinus aneurysm. Angiocardiography will establish the diagnosis.

Syphilitic Unperforated Aortic Sinus Aneurysms

Pathologic Aspects. Syphilitic involvement of the cardiovascular system is commonest at the

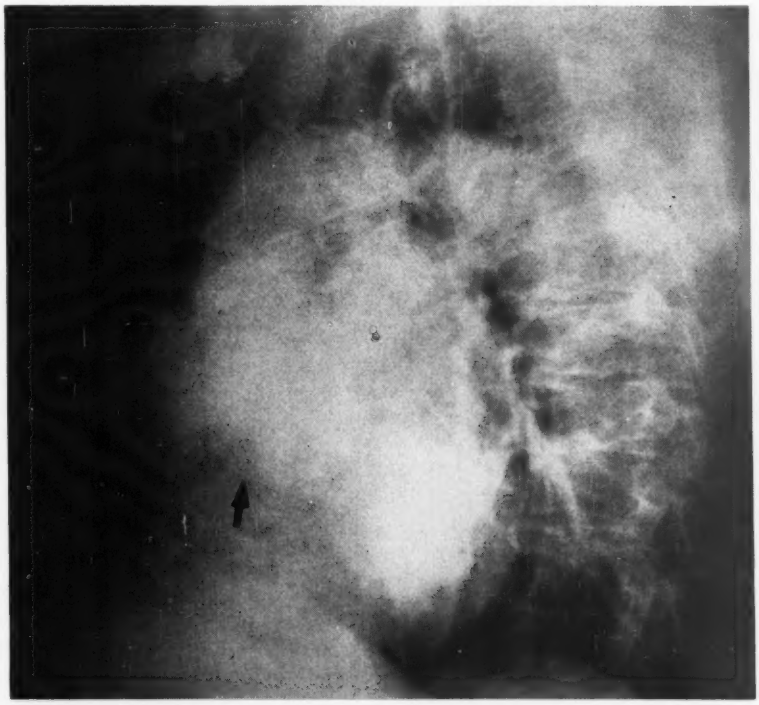


Fig. 4. Left anterior oblique angiocardiogram reveals the localized aortic sinus aneurysm (arrow) surrounded by calcified thrombus. The left ventricle is enlarged. (Previously published,[5] reproduced with the permission of the American Journal of Medicine.)

aortic valve and ascending aorta. It begins with weakening and destruction of the intimal surface of the aorta and elastic fibers of the media. The aortitis becomes manifest as either a diffuse aneurysmal dilatation or a localized saccular aneurysm of the ascending aorta. Calcium plaques are frequently deposited in the damaged intima; their recognition in the root and ascending aorta becomes an important clue of syphilis.[11, 12] If the aneurysm is large, stasis of blood occurs and a laminated thrombus partially fills the lumen. The aortic sinuses may similarly be involved and aneurysmal dilatation or sacculation of the sinuses results. Dilatation of the aortic ring and the production of aortic insufficiency are usual.[5]

Unlike congenital and mycotic aneurysms of the aortic sinuses, which are paper thin and prone to rupture,[1] syphilitic aneurysms usually become very large and laminated before they perforate.[1, 12] Any of the aortic sinuses may be the site of origin of a syphilitic aneurysm. This is in contrast to the congenital type, which is believed to involve chiefly the right and non coronary sinuses.[1] Contrary to reports, there is no predictable relation between the sinus of origin and the structure into which an aneurysm perforates.[13] Eight of the 11 perforated cases reported in the literature (73 per cent) ruptured into the lesser circulation (pulmonary artery 4, right atrium 2, and right ventricle 2), and produced a left to right shunt.[5] Syphilitic aortic sinus aneurysms, unlike the congenital, may also rupture outside the heart. This is probably

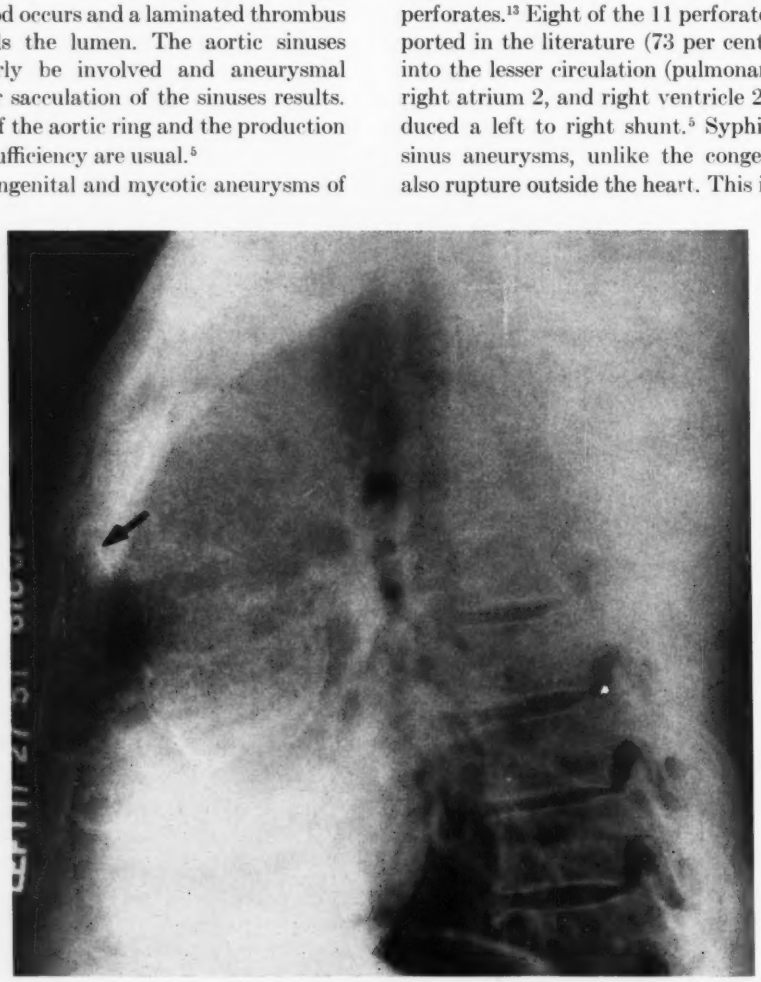


FIG. 5. Syphilitic saccular aneurysm of the ascending aorta with aneurysmal involvement of the aortic sinuses. Conventional lateral roentgenogram of a 53-year-old man shows enlargement of the left ventricle and a large saccular aneurysm of the ascending aorta, lined by calcium (arrow). Note that the linear calcification extends into the intracardiac portion of the aorta and clearly outlines the dilated aortic sinuses.

ecause the syphilitic aneurysms attain such a rge size.

In the literature, the most common cause of eath in patients with syphilitic aortic sinus neurysm, even with perforation, was heart ailure. Rupture in 8 cases with the establishment of aorticocardiac or aorticopulmonary hunts hastened failure; none survived more han 2 months. On the other hand, rupture utside of the heart caused sudden death. In 3 nstances, a coronary artery occlusion due to ressure of the adjacent aortic sinus aneurysm was present. In 1 case, myocardial infarction was found distal to the occluded left coronary artery and caused sudden death. In another, the aneurysm was intact but bulged into the interventricular septum and pulmonary conus causing pulmonary stenosis and delayed atrioventricular conduction, presumably due to pressure on the bundle of His.[5]

Clinical Aspects of Syphilitic Unperforated Aortic Sinus Aneurysms

Age, Sex, and Race. In our series of 10 cases of syphilitic aortic sinus aneurysms, all the aneurysms were unperforated. The ages ranged from 44 to 60 years and averaged 54 years. Men predominated; only 1 patient was a woman. Five were white and 5 Negro.

Symptoms and Signs. As a rule, prior to rupture, aortic sinus aneurysms do not by themselves produce symptoms. Rather, syphilitic involvement of the aortic valvular ring causes aortic insufficiency and heart failure. Most of our 10 patients were moderately to severely ill; all had aortic incompetence. Aortic diastolic and systolic murmurs, pounding pulses, and wide pulse pressures were usual. In 3, heart failure was present in addition. Pre-

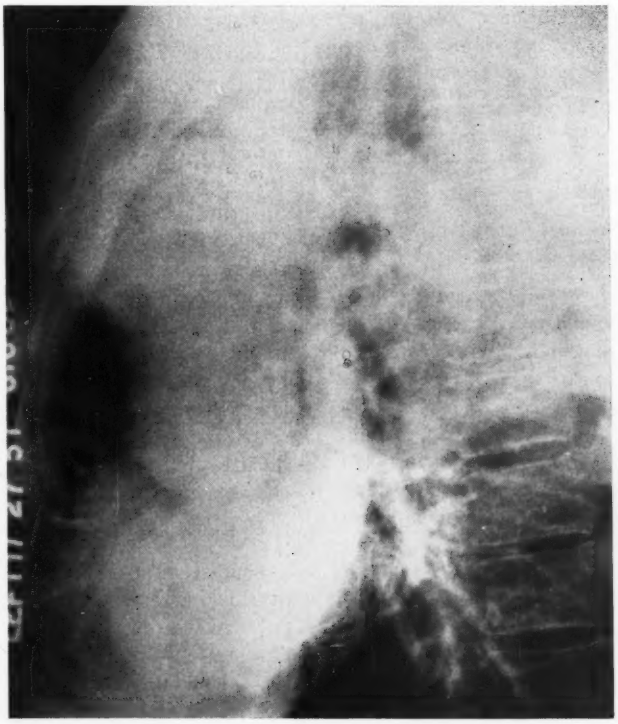


FIG. 6. Left lateral angiocardiogram demonstrates the aneurysm of the aortic sinuses, the dilated ascending aorta (aortitis) and the sacculated retrosternal aneurysm of the aorta. (Previously published,[5] reproduced with the permission of the American Journal of Medicine.)

cordial pain probably due to coronary ostial stenosis occured in several.

Blood Pressure. Prominent features in the reported cases and in our cases of syphilitic aortic sinus aneurysm were systolic hypertension, high pulse pressures, and low diastolic pressures, which were related to the aortic insufficiency. Two of our patients, however, had normal blood pressures.

Electrocardiography. Electrocardiographic examination in 9 living cases showed either left axis deviation or left ventricular hypertrophy. These findings reflect the enlargement of the left ventricle due to aortic regurgitation and hypertension. In 1 patient (fig. 3 and 4), there was right axis deviation and first degree heart block. In this instance compression of the pulmonary conus, pulmonary artery, and its right branch by the aneurysm was demonstrated, and is believed to have caused chronic cor pulmonale.[5] In the literature, 2 cases also exhibited right axis deviation of the electrocardiogram, but this was associated with perforation of the aortic sinus aneurysm into the lesser circulation. The right axis deviation in those instances was probably due to acute cor pulmonale from the overloading and hypertension of the right heart.[5]

Roentgenography of Syphilitic Unperforated Aortic Sinus Aneurysms

Conventional Roentgenography. The diagnosis of syphilitic aortic sinus aneurysm can often be made after conventional roentgenography. A large boot-shaped heart due to the large left ventricle caused by the isolated aortic insufficiency was present in all but 1 case. Pulsatile dilatation of the ascending aorta and fusiform or saccular aneurysms of the ascending aorta are other frequent findings. Linear calcification of the aorta is common and has long been recognized as an important sign of syphilitic aortitis.[11, 12] When the calcification extends into the intracardiac origin of the aorta and outlines the aortic sinuses (fig. 5 and 6), or becomes massive in this region (fig. 3 and 4), the diagnosis of syphilitic aortic sinus aneurysm becomes almost a certainty.

Rarely, a patient with right heart enlargement, right axis deviation of the electrocardiogram, and calcification near the left atrium may be mistaken for rheumatic heart disease with mitral and aortic valvular involvement and left atrial calcification.[5, 12] However, the presence of linear calcification in the ascending aorta should suggest the syphilitic etiology.

Angiocardiography. Aortic sinus aneurysms are readily demonstrated by angiocardiography. In the syphilitic, 2 types are recognized: in 7 instances, the aneurysms were continuations of huge fusiform or saccular aneurysms of the ascending aorta (fig. 6); in 3, the aneurysms were localized at the aortic sinuses and associated with aortitis (fig. 4). In all instances, the syphilitic aneurysms were considerably larger than the congenital types and, therefore, created pressure effects in the surrounding cardiac chambers and great vessels. In 1 case (fig. 3 and 4), the deformity of the pulmonary conus and the pulmonary artery and its left branch was sufficient to cause right ventricular hypertrophy and chronic cor pulmonale.[5]

In *summary*, the presence of a syphilitic aortic sinus aneurysm should be suspected whenever a fusiform or saccular aneurysm of the ascending aorta seems to extend into the heart. If, in addition, there is linear calcification of the ascending aorta reaching into the intracardiac origin of the aorta and, especially, if there is linear or massive calcification in the region of the aortic sinuses, the diagnosis of a syphilitic sinus of Valsalva aneurysm becomes almost a certainty. Angiocardiography by outlining the root of the aorta will make the definitive diagnosis and will establish whether the aortic sinus aneurysm is continuous with an ascending aorta aneurysm or localized, producing pressure on the neighboring cardiac chambers and great vessels.

Rupture of Aortic Sinus Aneurysms

Sudden onset of severe dyspnea, right heart overloading and failure, enlargement of the pulmonary artery, and evolution of machinery-like murmurs may mean rupture of an aortic root aneurysm into the pulmonary artery or right heart chambers.[14] Confirmation may be had by cardiac catheterization.[15, 16] A recent attempt to repair a ruptured aortic sinus was not successful.[17]

Treatment and Prognosis of Aortic Sinus Aneurysms

Surgical repair of syphilitic sinus of Valsalva aneurysms is formidable because of their large size and serious pressure effects on the neighboring cardiovascular structures. However, in the very rare congenital type (fig. 1) when the aneurysm is localized to a single aortic sinus, approach through the right atrium appears feasible. In our case, surgery of the aneurysm appeared especially dangerous because of the associated aortic regurgitation, coarctation of the aorta, and the recent bacterial endocarditis. However, the patient withstood surgical correction of the aortic coarctation very well.[7] Even though congenital sinus of Valsalva aneurysms are paper thin and tend to rupture, surgical repair of the diffuse aneurysmal types of unruptured congenital sinus of Valsalva aneurysms does not seem warranted.

Early diagnosis and treatment of syphilis will prevent aortitis and aneurysms. Evidence is being accumulated that penicillin treatment of aortitis, either simple or complicated by aneurysm, is also beneficial. Of our 10 cases of syphilitic aortic sinus aneurysm, 3 are dead, 3 were lost to observation, and 4 are alive and well and have been under medical care for periods up to 5 years.

The 9 patients with congenital types of aortic sinus aneurysms are all alive. The 4 with coarctation of the aorta had resection of the coarcted segments with complete relief of hypertension after end-to-end anastomosis of the aorta; all but the patient with recent subacute bacterial endocarditis are well and working. One of the 3 patients with arachnodactyly is still troubled by mild congestive heart failure; the other 2 continue to be free of cardiovascular complaints. The patient with pseudocoarctation is also free of cardiovascular symptoms and is working; while the child with the multiple valve disease and heart enlargement remains disabled.

The long-term prognosis of patients with unperforated aortic sinus aneurysms is unknown. However, even though there have been only a few years of observation, the general well being of the majority of our patients suggests that the prognosis is not immediately fatal. Once the aneurysm ruptures, the situation is usually hopeless. Therefore, even though the surgical approach is difficult and hazardous and the circulatory hemodynamics are desperate, an attempt to repair the perforation should be made.

Summary

There are no diagnostic features for the recognition of unperforated aortic sinus aneurysms except for a grade 3 to 4 cardiac murmur. Linear or massive calcifications in the intracardiac portion of the root of the aorta continuous with the linear calcifications of the ascending aorta sometimes occurs in syphilitic aortic sinus aneurysms. Accordingly, a high index of suspicion and angiocardiography are advocated in order to establish the diagnosis during life.

Surgical repair of a localized congenital aortic sinus aneurysm through the right atrial approach seems feasible if there are no serious complicating aortic or cardiac lesions. The diffuse unruptured aneurysmal congenital and syphilitic aortic sinus aneurysms are better left alone. If rupture occurs, surgical repair, even though heroic, should be attempted.

Addendum

Since this review was submitted for publication 5 more congenital aneurysmal dilatations of the aortic sinuses have been discovered. Four were associated with Marfan's syndrome (2 in identical twins 2 years old), the fifth with coarctation of the aorta.

Two recent reports from England also describe operations in 2 patients for closure of perforated congenital aortic sinus aneurysms.[18,19]

Summario in Interlingua

Il non ha characteristicas diagnostic pro le recognition de non-perforate aneurysmas del sino aortic, excepte un murmure cardiac de grado III a IV. Calcificationes linear o massive in le portion intracardiac del radice aortic, continuante in le calcificationes linear del aorta ascendente, occure a vices in syphilitic aneurysmas del sino aortic. Ergo, un alte grado de suspicion e le uso de methodos angiocardiographic es recommendabile si on vole establir le diagnose durante le vita del patiente.

In le absentia de serie aortic o cardiac lesiones complicatori, il pare practicabile reparar un localisate e congenite aneurysma del sino aortic via le atrio dextere. In casos de diffuse non-rupturate aneurysmas del sino aortic, tanto congenite como etiam syphilitic, il vale melio abstener se de omne intervention. Si un ruptura se effectua, le tentativa de un reparo chirurgic debe esser interprendite, ben que un tal es alora heroic.

REFERENCES

[1] Jones, A. M., and Langley, F. A.: Aortic sinus aneurysms. Brit. Heart J. **11:** 325, 1949.

[2] Venning, G. R.: Aneurysms of the sinus of Valsalva. Am. Heart J. **42:** 57, 1951.

[3] Falholt, W., and Thomsen, G.: Congenital aneurysms of the right sinus of Valsalva, diagnosed by aortography. Circulation **8:** 549, 1953.

[4] Basabe, H., Hojman, D., and Rósembilt, E.: Bicuspid aortic valve and aortic (Valsalva) sinus aneurysm opening into right auricle: Embolic gangrene of the left foot. Rev. Asoc. méd. argent. **68:** 173, 1954.

[5] Merten, C. W., Finby, N., and Steinberg, I.: The antemortem diagnosis of syphilitic aneurysm of the aortic sinuses: Report of nine cases. Am. J. Med. **20:** 345, 1956.

[6] Dubilier, W. H., Taylor, T. L., and Steinberg, I.: Aortic sinus aneurysm associated with coarctation of the aorta. Am. J. Roentgenol. **73:** 10, 1955.

[7] Steinberg, I., and Finby, N.: Congenital right aortic sinus aneurysm associated with coarctation of the aorta: Antemortem report of a case. New England J. Med. **253:** 549, 1955.

[8] —: Aneurysm of the aortic sinuses with pseudocoarctation of the aorta. Brit. Heart J. **18:** 85, 1956.

[9] —, and Geller, W.: Aneurysmal dilatation of aortic sinuses in arachnodactyly: diagnosis during life in three cases. Ann. Int. Med. **43:** 120, 1955.

[10] Dotter, C. T., and Steinberg, I.: Angiocardiography. New York, Paul B. Hoeber, Inc., 1951.

[11] Walkin, A.: The significance of calcification in the ascending portion of the aortic arch. Radiology **62:** 101, 1954.

[12] Shipp, J. C., Crowley, L. V., and Wigh, R.: Aortic sinus aneurysm: Production of intracardiac calcification and pulmonary artery fistula. Am. J. Med. **18:** 160, 1955.

[13] Ostrum, H. W., Robinson, B. D., Nichols, C. F., and Widman, B. P.: Aneurysms of the aortic sinuses or sinus of Valsalva. Am. J. Roentgenol. **40:** 828, 1938.

[14] Herrmann, G. R., and Schofield, N. D.: The syndrome of rupture of aortic root or sinus of Valsalva aneurysm into the right atrium. Am. Heart J. **34:** 87, 1947.

[15] Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1955, p. 442.

[16] Edwards, J. E., Bean, L. M., and Burchell, H. B.: Aneurysms of aortic sinuses: Anatomic, pathologic, clinical and physiologic studies in four cases, in three of which rupture occurred. Abstracted, Circulation **12:** 700, 1955.

[17] Kirklin, J. W.: Quoted by Burchell, H. B., Unusual forms of heart disease. Circulation **10:** 574, 1954.

[18] Oram, D., and East, T.: Rupture of aneurysm of aortic sinus (of Valsalva) into the right side of the heart. Brit. Heart J. **17:** 541, 1955.

[19] Brown, J. W., Heath, D., and Whitaker, W.: Cardioaortic fistula: A case diagnosed during life and treated surgically. Circulation **12:** 819, 1955.

CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.
Associate Editor: RAYMOND D. PRUITT, M.D.

Systemic Lupus Erythematosus

By JOSEPH J. BUNIM, A. MCGEHEE HARVEY, ALFRED J. BOLLET, T. F. HILBISH, EUGENE VAN SCOTT, LEON SOKOLOFF, AND GEORGE BRECHER

DR. JOSEPH J. BUNIM: The patient whose course we shall discuss today offers an unusual opportunity to study the history of lupus erythematosus. The life history of this child is almost coincident with the natural history of this disease. We are grateful to Dr. Bernard Benjamin of Brooklyn, New York, for this referral, and for his accurate and complete records.

Dr. Alfred J. Bollet: The patient is a 7-year-old girl admitted to the Clinical Center with a history of intermittent febrile episodes accompanied by arthritis of 4 years' duration.

At the age of 2½ months, following an episode of pneumonia treated with penicillin, the patient developed an erythematous rash on the cheeks and nose and a persistent cough. This rash has varied in severity but has never entirely disappeared. At the age of 2 years she developed deformed, thickened fingernails and clubbing of her fingers, which have also persisted. Frequent cultures of the nails failed to reveal fungi, and the cause of these changes remained obscure.

At the age of 3 years, redness, swelling, tenderness, and pain on motion of the right knee appeared for 24 hours, and 3 months later fever and painful swelling of both elbows and the left wrist. Within a week there were stiffness of the spine and pain in the temporomandibular joints. Subsequently, the feet, knees, and ankles were involved. The rash on her face spread and became more erythematous. Diagnoses of Still's disease and discoid lupus erythematosus were made.

Treatment with cortisone abolished the fever; the joint symptoms and the rash subsided but did not entirely disappear. Facial rounding and edema developed, but the dose of cortisone could not be lowered below 200 mg./day without return of joint pain and some fever. This regimen was continued for 2 years, when hydrocortisone was substituted in a minimum maintenance dose of 60 mg./day. Because of persistent activity of the disease process, an L.E. cell preparation was done, but was negative. The patient was referred to the Clinical Center for treatment with the new steroids.

Her past history was negative except for measles at age 4 and varicella at age 5. There was no family history of arthritis or related diseases.

On examination at the time of admission, the patient was a very small, thin, alert white girl in no discomfort, but coughing occasionally. The blood pressure was 110/70 mm. Hg, temperature 98.7 F., pulse 110. There was an erythematous rash on the left cheek and left elbow that was slightly raised and indurated and showed dilated follicular pores, follicular keratoses, and some central atrophy. Small acneform lesions were also present on the face. A rough, reddened patch was present on the hard palate. Small cervical, axillary, and inguinal nodes were palpable. No retinopathy was noted. Moist rales were heard over the right middle lobe. The heart was negative, the liver and spleen were not palpable, and there was no swelling or tenderness of any joint. There was clubbing of the fingers with dystrophic and hypertrophic nail changes (fig. 1).

Laboratory data at the time of admission included a normal urinalysis, hematocrit value of 42 per cent, white blood cell count of 13,200, with 87 per cent polymorphonuclear cells and

From the U. S. Department of Health, Education, and Welfare, U.S. Public Health Service, Bethesda, Md.

FIG. 1. Dystrophic and hypertrophic nail changes in a patient with systemic lupus erythematosus.

1 metamyelocyte (subsequently 4,700–8,300, with similar differential count), sedimentation rate 53 mm./hr. (Westergren), C-reactive protein negative, blood urea nitrogen 12 mg. per cent, fasting blood sugar 56 mg. per cent, sodium 140, potassium 4.6, chlorides 104 mEq./L., CO_2 26 mEq./L., calcium 10.5, phosphorus 4.4 mg. per cent, alkaline phosphatase 2.2 B-L units; albumin 3.6, globulin 4.4 Gm. per cent, and bilirubin 0.4 and uric acid 2.3 mg. per cent. Roentgenograms revealed areas of fibrosis and reticular mottling in both lung fields, some delay in bone development, and negative gastrointestinal tract. Electrocardiogram was normal.

It was thought that the patient had developed systemic lupus erythematosus. The L.E. preparation had been negative in the past, but after 2 negative tests, 3 subsequent smears were positive. The pulmonary findings could be part of systemic lupus or could be related to chronic pulmonary infection following the episode of pneumonia in infancy.

Following initial observations, the dose of hydrocortisone was lowered. At a level of 30 mg./day she developed indurated, erythematous, slightly tender areas about both elbows. At 10 mg./day the manifestations of lupus flared up, with fever to 100.7 F., marked malaise, severe anorexia, and diffuse aches and pains that were most marked in the joints. The facial rash spread, and a 0.5 cm. superficial ulceration appeared in the right buccal mucosa. The cough increased in severity, and fine, moist rales were heard throughout both lung fields. Tenderness was noted over all joints with swelling about the elbows. The sedimentation rate rose to 88 mm./hr. (Westergren), and the C-reactive protein became 1+. The hydrocortisone was abruptly discontinued, and prednisone, 20 mg./day, was given. There was dramatic improvement, with an abrupt end to the fever, malaise, pain, and anorexia. The joint tenderness subsided, the rales diminished, and the facial rash and mucous membrane lesions gradually faded. The dose of prednisone was subsequently lowered to 15 mg. daily, and the patient continued to do well. She has become completely asymptomatic and remains well at this time.

Dr. T. F. Hilbish: This patient has small, reticular infiltrative lesions throughout both lung fields, most marked in the lower lobes and particularly on the left. The lung fields show very small linear bands of fibrosis. The heart is within the upper limits of normal.

The only other radiologic finding is retardation in bony development. Practically all the joints that were x-rayed showed some delay in bony growth. For example, the head of the radius is very small and undeveloped for the patient's age. X-rays of the bones in hands and feet also show developmental retardation.

Dr. Bunim: There are several points in this patient's story that are worthy of comment. First, how soon could the diagnosis of lupus erythematosus have been made from the clinical features?

She started with a pulmonary infection that was considered to be pneumonia and was treated with penicillin. This was soon followed by an erythematous rash. We have no direct information on this earlier infection, but we do have some notes from the physician who saw her at the age of 2 years and 9 months for a recurrence of pulmonary infection.

According to these notes, there were dullness and bronchial breathing over the left lobe of the lung posteriorly. A presumptive diagnosis of pulmonary tuberculosis was supported by a positive patch test, later shown to be a false positive reaction. X-ray of the chest showed enlargement of both hilar regions and numerous areas of infiltration in both lung fields, especially the left. The spleen was palpable 3 fingerbreadths below the costal margin, the white count was 5,200, and the sedimentation rate was markedly elevated. Within 14 days after this examination the patient developed polyarthritis, which persisted for several years.

It seems, in retrospect, that the diagnosis could have been made at this time on the basis of repeated nonspecific pulmonary infections, splenomegaly, mucocutaneous eruption and erythematous skin rash, absence of leukocytosis, markedly elevated sedimentation rate, and polyarthritis.

Polyarthritis occurs in many patients with lupus erythematosus. Perhaps only half of them have joint pains and the other half have objective joint changes that may resemble acute rheumatic fever or a nondescript type of arthritis, but are most often indistinguishable from rheumatoid arthritis. For 2 years this child was considered a case of juvenile rheumatoid arthritis or Still's disease. We now search for L.E. cells routinely at this institution in all cases of rheumatoid arthritis.

The nail changes are interesting. We have been unable to find any reference in the literature to nail changes in lupus erythematosus, but we have seen 2 other patients with systemic lupus at the Clinical Center with similar nail changes.

Dr. Benjamin, who referred this child to us, reports that with cortisone therapy the liver became enlarged and was 2 to 3 fingerbreadths below the costal margin. For a time the patient received cortisone in doses of 200 mg./day.

In a study of 38 children with rheumatic fever treated with cortisone, we were impressed that children, especially under 8 years of age, are likely to develop hepatomegaly as a side effect of cortisone. In about 50 per cent the liver became palpable at the end of the first week and remained enlarged for several weeks to several months after the drug was discontinued. Liver biopsies have shown fatty infiltration.[1] Why adults escape this effect I do not know; but it is important in the management of children with rheumatic fever, for the large liver may be misinterpreted as evidence of congestive heart failure.

We have also seen marked liver enlargement as a result of prednisone treatment in children with acute rheumatic fever or rheumatoid arthritis. Therefore, I think this side effect will probably be seen commonly in prednisone, cortisone, and hydrocortisone therapy.

In our other patients with lupus erythematosus, prednisone had about 4 times the potency of cortisone (by weight). One patient required 150 mg. of cortisone plus 40 units of corticotrophin daily for control of symptoms, but as little as 5 mg./day of prednisone was adequate. Because the drug requirement was so low, it was discontinued, whereupon the patient immediately developed a relapse. Now he is very comfortable again on 10 mg. of prednisone daily. Several physicians have reported similar experiences.

Even with 60 Gm. of hydrocortisone, this child continued to have active disease, for which she was referred to the Clinical Center. Now she is completely symptom-free at 15 mg. of prednisone daily, a 4:1 ratio, but the control is maximum rather than barely satisfactory. It remains to be seen whether she will require more prednisone when she goes home and becomes more active.

Finally, I would like to discuss the question of transition from discoid lupus to systemic lupus erythematosus. The impression that discoid lupus does not go on to systemic lupus is not true. As early as 1937, Dr. Keil of New York noted a transition from the discoid to the systemic type, with clinical and histopathologic confirmation. In our own limited experience we have seen 6 such patients; the interval from the appearance of discoid to systemic lupus ranged from 2 to 31 years. In Dr. Harvey's series there were 3 such patients. Patients with a discoid lesion should therefore be followed very carefully as potential cases of systemic lupus.

If a patient has both systemic lupus erythematosus and an intercurrent infection like pneumonia and is treated with antibiotics alone without concomitant adrenal cortical steroids of some type, he may succumb. Consequently, it is extremely important to keep patients with discoid lupus under surveillance and to administer steroid therapy at the first sign of severe systemic involvement.

Dr. Eugene Van Scott: Lupus erythematosus was first described, roughly 125 years ago, when medicine was largely a descriptive science. The definitive descriptions of the gross, and later microscopic, characteristics of the skin lesions are examples of astute, detailed obser-

vations. The disease was first recognized as a primary skin disease, manifested by chronic patches of scaling erythema that often eventuated into scarring and atrophy of the involved skin. About 50 years later the disseminated form of the disease was described. It was noted that a certain number of individuals with skin lesions acquired a serious systemic illness.

Without precise figures, I think we can reasonably agree that the chronic discoid form tends to remain confined to the skin, with a very small percentage eventuating in the systemic disease. Whether to stress and study the similarities of these two states and their transitions or to stress and study their differences is perhaps of more than theoretic interest; the current tendency is to study the similarities. An important clue to the more serious systemic illness may lie in the fact that so many chronic discoid cases never disseminate.

One particular phenomenon found in this condition, ultraviolet sensitivity, is important at least in stimulating further thought. It is common knowledge that exposure to sunlight has a pronounced adverse effect on patients with either systemic or localized cutaneous lupus erythematosus. Indeed, some subjects without L.E. develop skin eruptions from sunlight, and microscopically the lesions are indistinguishable from L.E. One of the effects of ultraviolet light in suberythema general body exposures is to produce a picture that resembles adrenal insufficiency. These effects include a fall in blood pressure lasting 24 hours, a low fasting blood sugar, a flat glucose tolerance curve, and an increased readiness to skin pigmentation. Is this observation related to why L.E. is made worse by ultraviolet light and is improved by adrenal steroid therapy?

Second, light sensitivity is pronounced in pellagra, in which the chronic skin eruption grossly and microscopically often resembles lupus erythematosus. We know that this photosensitivity is related to a nicotinic acid deficiency. The classic corn diet possesses a pyridine-containing antagonist of nicotinic acid. Sulfapyridine is also a competitor of nicotinic acid, and the sulfa drugs as a group are capable of inciting or exacerbating cases of L.E., and of photosensitizing normal skin. From this chain of relationships arises the obvious question whether L.E. is related to defective metabolism of nicotinic acid or tryptophane, a normal precursor of nicotinic acid. Would some related compound be useful in the treatment of lupus erythematosus?

Third, it has been shown that ultraviolet light causes loss of specific absorption spectra of purines and pyrimidines, and depolymerizes desoxyribose nucleic acid. Very probably a depolymerization of DNA occurs in L.E., accounts for some histologic changes in several tissues, and is also a biochemical prerequisite for the L.E. phenomenon and the L.E. cell.

Several phenomena, then, suggest that the metabolism of nicotinic acid, nucleic acids, and the function of the adrenal cortex may be somehow interrelated in the biochemical pathology of lupus erythematosus.

Dr. Naomi Kanof: I would like to discuss 2 aspects of this disease in the patient presented. One concerns the nail changes. I have never seen a patient whose disease onset was as early as in this child, and I am therefore not able to recall changes of similar nature. But in adult patients this bulbous distortion of the fingers is not uncommon, and is an unfavorable prognostic sign, suggesting an acute process.

Every internist and dermatologist who is concerned with this disease comes to a very firm conclusion regarding its evolution and then has an experience to shake his conclusion. One patient mentioned by Dr. Bunim was undeniably a case of chronic discoid lupus erythematosus. But the fact that the child was only 9 years old seemed noteworthy. Chloroquine therapy was started. Within 3 weeks the patient was desperately ill, one of the most severe cases of fulminating lupus erythematosus I have ever seen.

On the other hand one sees patients with polymorphous eruptions from light of 20 years' duration with histopathology indistinguishable from disseminated L.E., and with leukopenia, increased sedimentation rate, and a history of epilepsy. They may fare very well even on exposure to ultraviolet light.

This field is ripe not only for the biochemist, as Dr. Van Scott mentioned, but also for the immunologist.

Professor Flarer[2] of Padua University has pointed out that the degree of erythema is unrelated to the degree of scarring, and that the intensity of the disease is unrelated to the sequence of events in chronic discoid L.E. He has suggested that there are probably several types of erythema, a concept that may have an important relationship to the mechanisms of lupus erythematosus.

The second important consideration is that of Gold,[3] who considered the development of the L.E. cell an immunologic reaction. If this is a disease of immunologic mechanism, its course is unique. More common in progression of an immunologic disease is the process in syphilis, in which the invasion of organisms is followed by an acute reaction without destruction of tissue; after many years, the number of organisms lessens, the tissue response intensifies, and subsequently the tissue itself is destroyed. In lupus erythematosus the progression is from the indurated and scarring lesion to the disseminating and fulminating disease.

Dr. Leon Sokoloff: It is one of the peculiarities of disseminated lupus erythematosus that anatomic changes are inconstant, of varying character, and, in large part, lacking in diagnostic specificity. Virtually any organ may be involved. Not infrequently the pathologist is unable to detect appreciable changes in patients who have had the most profound clinical symptoms. Probably the most characteristic lesions are observed in the circulatory system—the heart, small arteries, arterioles, and glomerular capillaries. For purposes of simplification, the vascular lesions may be placed in 2 categories, the luminal and the mural, and they may be illustrated in the renal glomerulus.

The luminal change is characterized by formation of hyaline thrombi in some of the capillaries of the tuft. At one time, these thrombi were regarded as an extrusion of a mural deposit into the lumen. More recently, it has been recognized that the thrombi may be quite discrete (fig. 2) and occur independently of the so-called wireloop change in the walls of the capillaries (fig. 3). The hyaline material appears similar to fibrin and, for this reason, it is often referred to as a fibrinoid substance. A unique feature of the fibrinoid material in disseminated lupus erythematosus has been described recently by Dr. Klemperer and his associates in New York City as an inclusion of homogeneous material that is stained somewhat blue by

FIG. 2. Thrombi in some of the capillaries may be quite discrete.

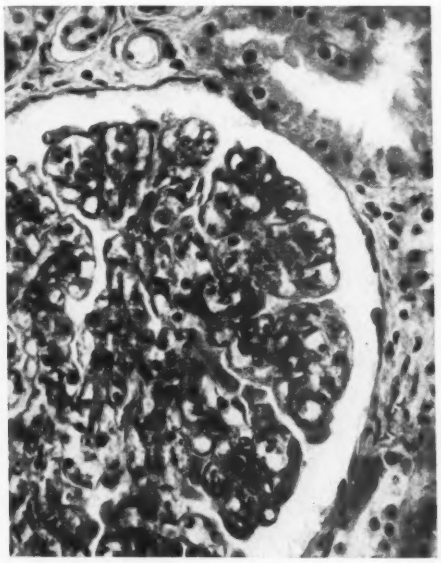


FIG. 3. Thrombi may occur independently of the so-called wire-loop change in the walls of the capillaries.

hematoxylin. According to these investigators, this "hematoxylin body" is derived from degraded cell nuclei; the desoxyribonucleoprotein becomes depolymerized progressively and is transformed, thereby, into the fibrinoid substance. The hematoxylin body corresponds to the central inclusion of the L.E. cell. When present, the body is regarded as a specific and characteristic feature of disseminated lupus erythematosus.

The mural change is characterized by the deposition of a fibrinoid substance in the wall of the capillaries and other vessels. Similar material may also be seen, at times, in extravascular connective tissues as well.

The sequence of events is interpreted morphologically by the group at Mt. Sinai Hospital as follows. Disseminated lupus erythematosus involves an abnormality of desoxyribonucleoproteins. Certain connective tissue cells die and their desoxyribonucleic acids become depolymerized. The fibrinoid substance resulting from this degradation is formed within the blood stream and finds its way into the walls of the blood vessels and surrounding tissues. There it evokes a variety of nonspecific inflammatory reactions. When the heart is involved, verrucous endocarditis, interstitial myocarditis, and pericarditis develop. In the visceral circulation, arteritis may appear, accompanied by a variable inflammatory reaction. In its most extreme forms, the arteritis cannot be distinguished from polyarteritis nodosa. In the kidneys, glomerulonephritis develops frequently.

Despite these observations, vascular lesions are not observed frequently in many of the lesions of lupus erythematosus. The cutaneous, choroid, muscle, and synovial lesions are inflammatory and rarely present vascular changes. It has long been recognized that waxing and waning pneumonia may dominate the clinical course of lupus erythematosus. At necropsy banal bacterial types of pneumonia, with or without organization, are frequent. Recently a number of observers have suggested that there is a more specific pattern of pulmonary inflammation in the disease, characterized by an interstitial reaction, with edema and inflammatory infiltration in the walls of the smaller air spaces. This interesting suggestion warrants further investigation.

Dr. George Brecher: The first set of L.E. preparations on this patient made from the buffy coat of heparinized blood was negative. The second set of preparations was positive, with both Hargraves' test on clotted blood and Conley's test[4] in which buffy coat smears are made from incubated, heparinized blood after rotation with added glass beads. In general, Conley's test appears to increase the amount of L.E. material, without necessarily increasing the number of L.E. cells. We believe Conley's test matches Hargraves' in sensitivity, but is more easily read because the amount of L.E. material serves as a signal to search assiduously for L.E. cells. Moreover, L.E. cells are more readily identified because of better preservation of cellular detail.

On occasion, L.E. material is plentiful and L.E. cells are not found. It is not known why L.E. material is phagocytized in one patient and not in another. Since it is not present in control subjects, it probably has some specific meaning. It seems best at this time, however, to require the presence of L.E. cells for a positive test. Occasionally only 1 or 2 L.E. cells are found in a single preparation even on repeated trials. To my knowledge, none of the numerous modifications of the L.E. test has solved the problems posed by the presence of L.E. material without L.E. cells or by the finding of a single positive test.

Dr. A. McGehee Harvey: During the last 6 or 8 years I have seen a great number of patients with this disease, and have developed a somewhat different concept of its natural history than is ordinarily described. I think that in many respects the patient we have seen today furnishes a good text for presenting this concept.

First of all, the course of this disease in the majority of the cases is a very chronic one. It is characterized by exacerbations and remissions. Furthermore, in any 1 exacerbation, only 1 or several organ systems may be involved. In this manner, the disease unfolds over a period of years with a number of seemingly unrelated episodes of illness, leading the unwary physician to overlook its presence for many years.

The appearance of chronic lesions, particularly on the face, for many years before any other manifestations of the disease appear, has been discussed today. Also, we have seen patients who had arthritis for many, many years before they developed other manifestations of the disease. One may observe patients in whom the disease apparently began with a hemolytic type of anemia or thrombocytopenic purpura or repeated epileptiform convulsions as the only clinical evidence of illness for as long as 10 or 12 years.

Remissions may last a long time and may vary in degree. The disease may go from a state of fulminating intensity to a period in which the patient is entirely free of any symptom for a long time.

We believe that this is probably a more common disease than any of us realize even now, and that it may go on for many years in a very mild relapsing course. An example is a patient who came into the hospital recently for treatment of severe hypertension. She had never had any complaints concerning her skin or any difficulty other than the hypertension, which developed following pregnancy. The intern who saw this patient knew that she was going to receive hypotensive drugs, one of which is accompanied at times by a rheumatic-like picture, occasionally with the finding of L.E. cells. He saw a very small erythematous lesion on the patient's forehead and ordered an L.E. cell test, which was positive.

Often the manifestations in the beginning are so vague that it is hard to date their onset. When a given manifestation appears, it is natural to make the diagnosis referable to that single organ system. As Dr. Bunim has already stated, many of these patients in the beginning are said to have rheumatoid arthritis.

Many physicians dismiss the possibility of systemic lupus erythematosus unless all the classical manifestations are present in a single period of activity of the disease, but we have seen patients who developed a skin lesion in the beginning and had cutaneous lesions for 10 or 12 years before they developed any other manifestations. Some patients had other manifestations for 10 or 12 years before they ever had any cutaneous lesions, and still other patients ran the full course of the disease without cutaneous manifestations at any time.

It is important, I think, to recognize the minor phases of the illness. For instance, the patient may say that he has always been sensitive to sunlight, or that all of his life he has had recurrent aches in his joints, although they were never severe enough to warrant consulting a physician. The patient may fail to describe a previous attack of pleurisy or a previous episode of cutaneous difficulty unless specifically asked about it because he does not recognize its possible relation to the current complaint.

The clinical diagnosis of systemic lupus, I think, can be made consistently only when the observer appreciates the chronic course of this disease, with episodic periods of illness that may seem entirely unrelated; and that with a disease apparently involving only a single system, such as arthritis, it is important to inquire specifically about previous illnesses that may be related. What has happened in the past may make the current event more meaningful.

Figure 4 shows the sex, race, and age incidence at onset in a number of patients that we have observed. I would like to call your attention to 2 points: most of the patients are females, and in most of them the disease begins in the second, third, or fourth decades.

Studies reported elsewhere[5] indicate the frequency with which various systems are involved in the total course of the illness in these

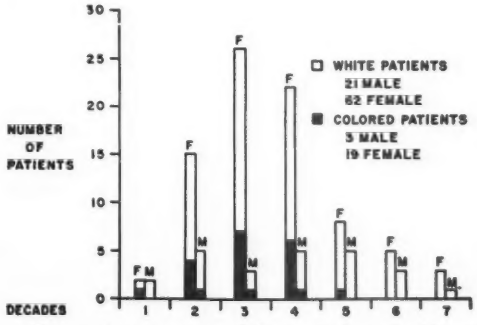


FIG. 4. Age at onset and the sex and race incidence in 105 cases of systemic lupus erythematosus. (From Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. Medicine **33:** 291, 1954, published by The Williams and Wilkins Company.)

patients. Joint manifestations are frequently seen. Cutaneous manifestations are also common, and it is important to point out that mucous membrane lesions do occur, as exhibited by this patient. Frequently there may be involvement of a wide variety of other organs.

One tends to think of skin lesions in relation to this disease as being those that are classically described, but the skin lesions are multiform. Almost any type of lesion may be seen. One thing that has impressed us greatly is the frequency of urticarial lesions and also of lesions resembling angioneurotic edema.

Reference has been made to pulmonary lesions. Dr. Hilbish described the common type of lesion, usually in the lower lung fields. Pulmonary changes are more frequent than has been commonly recognized. They may be chronic in nature. The symptoms of pulmonary difficulty are out of proportion to any objective findings on physical examination. The patient may be tachypneic, dyspneic, somewhat cyanotic, while on examination of the lungs only a few scattered rales may be heard. In going over all our films on these patients, we were impressed with the frequency of elevation of the diaphragm and plate-like areas of atelectasis in the lower portions of the lung fields.

Retinal cytoid bodies are commonly seen. They are exudative lesions in the nerve fiber layer of the retina that resemble cells microscopically. They are not specific for lupus. They have the same appearance as the cotton wool exudates in hypertensive disease and diabetic retinitis.

The patient presented today had a high serum globulin level. A striking feature of this disease is the frequency of abnormal protein changes in the blood. The patients almost uniformly have an elevated sedimentation rate and an elevated serum fibrinogen level. On several occasions a circulating anticoagulant has been demonstrated.

The elevation in serum globulin is frequent, particularly the gamma globulin fraction. A very large percentage of these patients have positive cephalin flocculation and positive thymol turbidity tests and other protein abnormalities. Of course, it is a protein in the serum that is responsible for the formation of the L.E. cell.

It has been known for many years that patients with systemic lupus may have a false serologic test for syphilis. With the advent of the treponemal immobilization test, it has become possible to recognize with certainty a truly false positive serologic test. In the series of patients we have observed, a false positive serologic test for syphilis was found in about 20 per cent of the cases.

Dr. J. Earle Moore[6] has been interested for a number of years in the persistent false serologic test for syphilis with the object of determining its significance. Not under consideration is the acute false positive test that develops in acute situations like malaria and pneumonia and disappears in a matter of a few weeks or months. Of private patients in the upper socioeconomic class tested by Dr. Moore, 40 per cent had a false serologic test for syphilis. In over 60 per cent of the cases the test was simply a routine examination. That is, the patient applied for a job, got married, had a baby, was inducted into the Army, or something of that sort, and all were in perfect health so far as they knew. Thirty-seven per cent had some type of illness, but it was usually a minor illness of vague nature for which the cause could be determined.

Dr. Moore and his group now have well over a hundred of these patients who have been classified as false positive reactors: they had no likely exposure to syphilis, had 2 negative treponemal immobilization tests, and had no evidence of syphilis on physical examination. The false positive test was chronic, in that positivity was known for 2 to 20 years, with an average of over 6 years.

The sex distribution of these false reactors is almost identical with that of the series of cases of proved lupus erythematosus I showed you previously. The age distribution for the discovery of the false positive serologic tests is similar to that for the onset of symptoms of lupus.

Of 44 men in Dr. Moore's series, 1 has developed known rheumatoid arthritis, 9 have developed a series of illnesses in which the diagnosis was probably collagen vascular disease,

TABLE 1.—*"Probable" Systemic Lupus Erythematosus: Clinical Manifestations in Twenty-One Patients.**

Symptom or sign	No. of cases showing specified symptom or sign
Fever	12
Arthralgia or arthritis	13
Ocular lesions	6
Splenomegaly; serositis; cutaneous lesions	5 each
Raynaud's phenomenon; significant malaise	4 each
Major phlebothrombosis; psychoses; nephritis	3 each
Photosensitivity; mucosal lesions; chorea; hematuria	2 each
Thrombocytopenic purpura; convulsions; nephritis	1 each

* From Moore, J. E., and Lutz, W. B. J. Chronic. Dis. *1:* 3, 1955, published by the C. V. Mosby Company.

Each patient has had at least 2 and usually several of the 17 manifestations listed; and the 21 patients have had a total of 75 of these symptoms or signs (i.e., 3.57 per patient).

and 1 now has systemic lupus proved by a positive L.E. cell test.

Of the 104 women, 9 have now developed proved systemic lupus erythematosus. By "proved" I mean that they have developed L.E. cells while under observation. Six have developed a clinical picture indistinguishable from rheumatoid arthritis. Another 36 have developed a series of illnesses that seem clinically to be systemic lupus erythematosus, but as yet no L.E. cells have been found. Furthermore, 43 of these patients also have developed some type of serum protein abnormality, usually an elevation of serum globulin.

Table 1 shows the clinical manifestations in the patients who have been classified as probably having systemic lupus erythematosus. There have been episodes of fever in 12 and episodes of arthritis or arthralgia in 13. Other manifestations included splenomegaly, serositis, and Raynaud's phenomena, which may develop in patients with systemic lupus.

Each of these patients has had at least 2, and usually several, of the 17 different manifestations listed, with an average of 3.8 episodes. An abnormal cephalin flocculation developed in 76 per cent, a positive thymol turbidity test in a large portion and elevation of the serum globulin level in a large portion.

One patient described by Moore started out with a protein abnormality of the blood (the false positive serologic test for syphilis), and 12 years later developed positive L.E. cell tests, with various illnesses in between. This sequence brings out a very important point in regard to the diagnosis of this disease and the determination of when there is local lupus, so to speak, and when there is systemic lupus. From this study of false biologic reactors it becomes obvious that the L.E. cell phenomenon may be a relatively late event in the disease, so that a negative L.E. cell test in no way excludes the diagnosis.

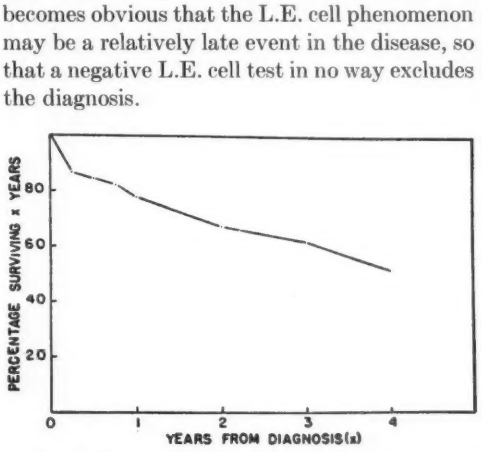


FIG. 5. Survival after diagnosis in 99 cases of systemic lupus erythematosus seen from 1949 through 1953. (From Harvey, A. M. and associates. Medicine **33:** 291, 1954, published by The Williams and Wilkins Company.)

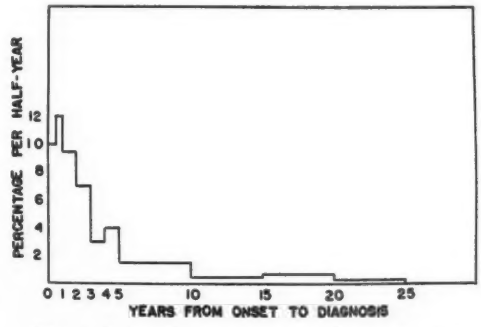


FIG. 6. Intervals from onset to diagnosis of systemic lupus erythematosus. (From Merrell, M. and Shulman, L. E., J. Chron. Dis. **1:** 12, 1955, published by The C. V. Mosby Company.)

Finally, I would like to review what has happened to a hundred of our patients, studied since 1949, who have been treated with one of the adrenal hormones during periods of activity of the disease. Figure 5 shows a survivorship curve that was constructed by Dr. Merrill of the Department of Biostatistics. The duration of disease in these patients was considered from the time the diagnosis was made, not the time of the first manifestation of illness.

In the first 3 months after diagnosis, 13 per cent of the patients died, but after that there has been a rather steady curve, which indicates that about 10 per cent of the original group have died each succeeding year. That leaves 52 per cent of these patients surviving a full 4 years after the diagnosis was made.

Dr. Ragan and his co-workers published an analysis of prognosis several years ago in which 38 per cent survived for 4 years from the time of onset of the first symptom until death. This 4-year survival of 38 per cent is considerably less than in our series; and ours is weighted in the opposite direction, since duration of life was calculated from date of diagnosis. Figure 6 shows the intervals of time from time of onset to time of diagnosis of the disease, illustrating again the chronic nature of this disease. Many of these patients had manifestations for 5, 10, or 15 years before the diagnosis was finally established.

REFERENCES

[1] Steinberg, H., Webb, W. M., and Rafsky, H. A.: Hepatomegaly with fatty infiltration secondary to cortisone therapy; case report. Gastroenterology **21:** 304, 1952.

[2] Flarer, F.: The causes of inflammatory erythema. J. Invest. Dermat. **24:** 201, 1955.

[3] Gold, S. C.: Some observations on the pathogenesis of systemic lupus erythematosus. J. Invest. Dermat. **19:** 333, 1952.

[4] Zinkham, W. H., and Conley, C. L.: Some factors influencing formation of L.E. cells: A method for enhancing L.E. cell production. Bull. Johns Hopkins Hosp., **98:** 102, 1956.

[5] Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, G. L., and Schoenrich, E. H.: Systemic lupus erythematosus; review of the literature and clinical analysis of 138 cases. Medicine **33:** 291, 1954.

[6] Moore, J. E., and Lutz, W. B.: The natural history of systemic lupus erythematosus: An approach to its study through chronic biological false positive reactors. J. Chron. Dis. **1:** 297, 1955.

Schreier, P. C., Adams, J. Q., Turner, H. B., and Smith, M. J.: Toxemia of Pregnancy as an Etiological Factor in Hypertensive Vascular Disease. J. A. M. A. **159:** 105 (Sept. 10), 1955.

A group of 239 patients with toxemia of pregnancy occurring during the first gestation has been followed from periods of 5 to 10 years. All but 11 had subsequent pregnancies. Although a higher percentage suffered recurrent toxemia, only 27 (or 11.3 per cent of the total) were found to have permanent hypertensive disease. The expected incidence of hypertension for young women of this age is 8.4 per cent according to Master and his group. The authors believe that in all likelihood this figure is higher than the true incidence of hypertensive disease in women of this age, because many of the observations of Master and his group were made at a time these women were applying for jobs and when slight elevation of blood pressure is common. The authors conclude that toxemia of pregnancy results in increased incidence of hypertensive disease, that the more severe the initial illness (excluding eclampsia) the more likely there is to be eventual permanent vascular damage. Repeated pregnancies and recurrent episodes of toxemia may have some relationship to the later occurrence in hypertensive disease, in that most women developing permanent elevation of blood pressure did so after 3 pregnancies and at least 2 bouts of toxemia.

Kitchell

ABSTRACTS

Editor: SAMUEL BELLET, M.D.

Abstracters

DAVID I. ABRAMSON, M.D., Chicago
DOMINGO M. AVIADO, JR., M.D., Philadelphia
ARTHUR BERNSTEIN, M.D., Newark
MASSIMO CALABRESI, New Haven
CHARLES D. ENSELBERG, M.D., New York
RAYMOND HARRIS, M.D., Albany
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
EUGENE LEPESCHKIN, M.D., Burlington
MORTON H. MAXWELL, M.D., Los Angeles
VICTOR A. MCKUSICK, M.D., Baltimore
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
FRANCIS F. ROSENBAUM, M.D., Milwaukee
ELLIOT L. SAGALL, M.D., Boston
DAVID SCHERF, M.D., New York
JOHN B. SCHWEDEL, M.D., New York
CHARLES R. SHUMAN, M.D., Philadelphia
FRANKLIN SIMON, M.D., Newark
LOUIS A. SOLOFF, M.D., Philadelphia
S. O. WAIFE, M.D., Indianapolis
RICHARD WECHSLER, M.D., Pittsburgh
MARTIN WENDKOS, M.D., Philadelphia
STANFORD WESSLER, M.D., Boston

CONGENITAL ANOMALIES

Fowler, N. O., and Mannix, E. P.: Estimation of the Size of the Patent Ductus Arteriosus from Hemodynamic Data. J. Clin. Invest. **34:** 1242 (Aug.), 1955.

A comparison was made between the diameter of a patent ductus arteriosus, as measured at operation, and certain preoperative hemodynamic observations. A significant association was found between the actual diameter of the ductus and the degree of increase in oxygenation of pulmonary arterial blood. The diameter was also related to the calculated volume of blood flow through the ductus. However, the calculated internal diameter was not a very accurate estimate of the true diameter, and the evidence suggests that the ductus does not behave as a perfect orifice. The possible sources of error are discussed.

WAIFE

Aitken, G. J.: The Wide Patent Ductus Arteriosus. Glasgow M. J. **36:** 175 (June), 1955.

In a series of 98 cases of patent ductus arteriosus the clinical features in 18 were unusual and were regarded as characteristic of a wide, often short, patent ductus arteriosus. The diagnosis has been confirmed at operation in the 16 cases subjected to operation. Various features differentiated these cases from the others. There was increased pulmonary and cardiac stress in the form of repeated respiratory infection, deformity of the thoracic cage, signs of forceful left ventricular action and of excessive blood flow through the left side of the heart, together with pulmonary vascular accentuation, hyperdynamic pulmonary arterial pulsation, and frequent right ventricular enlargement. Pulse pressure was high and in addition to a systolic or systolic-diastolic thrill to the left of the upper sternum, there was a systolic thrill in the suprasternal notch and often in the neck vessels. The associated murmur was always systolic-diastolic in type. In no case was it "machinery" in character.

Cardiac catheterization confirmed the presence of a wide patent duct by the ease with which the catheter passed into the aorta and by a high oxygen content of the pulmonary arterial blood. Passive pulmonary hypertension with a large pulmonary blood flow was the usual finding, but active pulmonary hypertension, secondary to increased pulmonary arteriolar resistance may develop, probably as a protective measure. Closure of the duct should be done early in cases of wide patency, if possible before irreversible myocardial or pulmonary vascular changes have occurred.

BERNSTEIN

Powell, M. L., and Hiller, H. G.: Pulmonary Coarctation. M. J. Australia **1:** 272 (Feb.), 1955.

A small, thin, 5-year-old boy was admitted to the Royal Children's Hospital, Melbourne, with a history of tiredness and inadequate weight gain. A long, almost continuous murmur was heard at the pulmonary area and the pulmonary second sound was split. Angiocardiography demonstrated narrowing of both right and left pulmonary arteries at the bifurcation of the main vessel. The main pulmonary artery proximal to the narrowing was dilated.

Cardiac catheterization showed a fall in pressure across the bifurcation of the pulmonary artery, the pressure in the right pulmonary artery being 15/5 mm. Hg; in the main pulmonary artery, 33/5.

The diagnosis of pulmonary coarctation was therefore made in this case. The condition is rare and is not as yet well understood; no explanation of its cause has been forthcoming.

BERNSTEIN

Friedman, S., Murphy, L., and Ash, R.: Congenital Mitral Atresia with Hypoplastic Nonfunctioning Left Heart. Am. J. Dis. Child. **90:** 176 (Aug.), 1955.

This is a review article summarizing the pertinent literature and presenting 6 case reports with necropsy findings of congenital mitral atresia. A pathologic classification is included. Clinically, there are no consistent physical signs except those of right-sided hypertrophy. Systolic murmurs over the base may be present. Classical physical signs of congestive failure, including tachycardia, tachypnea, hepatomegaly, and gallop rhythm, were present only terminally. Since the anatomic features permit only mixed arterial-venous blood in the splenic circulation, the absence of cyanosis, except where cardiac failure supervened, is noteworthy. When cyanosis appeared, death shortly followed. The authors believe that there are no classical clinical features that permit a premortem diagnosis. The defect is not compatible with life; death in these infants is usually within a week or month of birth.

HARVEY

Kittle, C. F., Diehl, A. M., and Heilbrunn, A.: Anomalous Left Coronary Artery Arising from the Pulmonary Artery. J. Pediat. **47:** 198 (Aug.), 1955.

A case report is presented of a 3-month-old boy who had signs of heart failure. Irritability and crying after feeding were noted in the second month of life. He was pale, had cardiomegaly, and was in respiratory distress. The electrocardiographic pattern showed a deep Q wave and depression of the S-T segments. A diagnosis of anomalous left coronary artery was made and surgical exploration was begun, but the child died early in the operation. At necropsy the diagnosis was confirmed. The symptoms were thought to be due to anoxia caused by progressive decrease in blood supply to the left ventricle with the closure of the ductus arteriosus and subsequent fall in pulmonary artery pressure from the high level existing in fetal life. Previously reported cases are reviewed.

HARVEY

Seaman, W. B., and Goldring, D.: Coarctation of the Aorta with Patent Ductus Arteriosus. J. Pediat. **47:** 588 (Nov.), 1955.

Four cases of coarctation of the aorta associated with patent ductus arteriosus in infants are presented. Three cases came to autopsy. In addition, data on another 8 cases are included. This condition is reported to be a common cause of cardiac failure and death in infancy. The roentgenologic features of these cases were suggestive of ventricular hypertrophy, enlargement of the pulmonary arteries, and indentation of the aorta on the left border. Clinically, the blood pressure difference between the upper and lower extremities, as well as differential cyanosis in the extremities, was a helpful sign. The prognosis is poor without surgical intervention, and currently the results of surgery are far from good.

HARVEY

Grosse-Brockhoff, F., Mürtz, R., and Neuhaus, G.: Polycythemia as a Compensating Factor in Morbus Coeruleus. Ztschr. Kreislaufforsch. **44:** 700, 1955.

In 200 cases of Fallot's tetralogy, trilogy, or pulmonary atresia, there was an almost linear relation between the decrease in the oxygen saturation of the arterial blood and the hemoglobin concentration. The actual cardiac output, determined through cardiac catheterization, was on the average 0.6 L./sq.M./min, less than the output calculated to be necessary to maintain the actual venous oxygen tension if the hemoglobin concentration were normal. This saving in the pulmonary blood flow by polycythemia is of great importance in the presence of pulmonary stenosis; a decrease in flow due to increased blood viscosity is considered of importance only when failure of the right ventricle appears. On the other hand, the venous oxygen saturation would, on the average, be 6 mm. Hg less at the same pulmonary flow if the hemoglobin concentration were normal. These relations are represented by nomograms.

LEPESCHKIN

Mürtz, R.: The Calculation of Relative, Percentile and Absolute Values of the Shunt in Patients with Congenital Heart Disease. Ztschr. Kreislaufforsch. **44:** 714, 1955.

Nomograms have been developed that allow instant determination of the relative shunt (expressed as a percentage of the nonshunted blood flow) from the oxygen saturations in the vena cava and a peripheral artery in the case of a right-to-left shunt; a very small error results from the assumption of a constant saturation in the pulmonary veins. Corresponding nomograms are given for calculation of the relative left-to-right shunt from the saturations in the vena cava and the pulmonary artery; in this case the error may be as much as 50 per cent. Copies of the nomograms may be obtained from the author.

LEPESCHKIN

Shoenmackers, J., and Stratmann, E.: The Coronary Blood Vessels and the Myocardium in Congenital Cardiovascular Malformations. Arch. Kreislaufforsch. **22:** 153, 1955.

In 60 cases of congenital heart disease the most common findings were dilated and hypertrophic coronary arteries and veins, dilated capillaries, numerous intracardiac and extracardiac anastomoses of the coronary arteries, and hypertrophy of the myocardial cells of the right ventricle without degenerative signs. The number of nerve cells was

considerably greater than in normal persons of the same age.

LEPESCHKIN

Peace, R. J.: Cor Pulmonale in Newborn Infants. Am. J. Dis. Child. **89:** 567 (May), 1955.

Newborn infants with severe atelectasis seldom survive long enough to develop secondary cardiac changes other than dilatation, but in rare instances survival is sufficiently prolonged to permit hypertrophy of the myocardium of the right ventricle, giving the heart the characteristic anatomic configuration of cor pulmonale as seen in older age groups. Because the clinical behavior of the atelectasis-cor-pulmonale lesion-complex can so closely simulate that of a congenital malformation of the heart, the correct etiologic diagnosis is often made only after death and examination of the lungs and heart at necropsy. This is a matter of more than academic interest, for there is evidence that resolution of the pulmonary lesion may sometimes lead to clinical recovery. Currently improved methods of treatment of atelectasis of the newborn will make possible longer periods of survival, so that the condition may be observed more frequently than in the past.

The present report is based on the pathologic findings in 2 cases studied at necropsy. Both infants were cyanotic at birth and had cardiac enlargement and loud systolic murmurs audible over the entire precordium, with death on the seventh and thirteenth day of life. Necropsy showed severe atelectasis of the lungs with secondary right-sided cardiac hypertrophy and incompetence. The mechanism is apparently one of peripheral compression of the capillary vascular bed by collapsed lung parenchyma, with impedance of pulmonary blood flow, dilatation of the chambers of the right side of the heart, and eventual hypertrophy of the myocardium. Death may be explained by the combined effects of both pulmonary and cardiac failure.

MAXWELL

Contro, S., and Brostoff, P.: Pulmonic Stenosis with Left-to-Right Ventricular Shunt. Am. Heart J. **50:** 543 (Oct.), 1955.

Eight patients with pulmonic stenosis and left-to-right ventricular shunt are reported. The salient clinical features were normal development, absence of cyanosis at rest, reasonably good adaptation to the congenital anomaly, and absence of clubbing. The vascularity of the lungs was normal, or increased, even when the second pulmonic sound was markedly diminished or absent. The classical murmur of pulmonic stenosis was heard. The electrocardiogram showed right-heart strain, usually associated with evidence of right bundle-branch block.

The importance of an accurate diagnosis of the existence of pulmonic stenosis, with a left-to-right ventricular shunt, lies in the facts that pulmonic valvulotomy or infundibular resection may be deleterious by producing a greater left-to-right shunt, and that shunting procedures should, at our present level of septal surgery, not be undertaken.

RINZLER

Philipson, J., and Saltzman, G. F.: Combined Ventricular Septal Defect and Aortic Insufficiency. Acta radiol. **44:** 269 (Oct.), 1955.

The authors report 6 cases with ventricular septal defect in which aortic valvular deformity occurred with resultant aortic insufficiency. All had murmurs suggestive of patent ductus arteriosus, left ventricular enlargement, increased amplitude of aortic pulsations, and increased oxygenation of right ventricular blood. Three of these diagnoses were confirmed at the time of thoracotomy, a fourth was confirmed at autopsy.

The suggestion is offered that the aortic valvular cusp riding above the high septum membranaceum is dynamically affected, but in some instances there seems to be evidence of inflammatory aortic valvular involvement as well.

SCHWEDEL

CORONARY ARTERY DISEASE

Bakst, A. A., Costas-Durieux, J., and Bailey, C. P.: Arterialization of the Coronary Sinus for the Revascularization of the Heart in Coronary Artery Disease. Mortality Study Following Circumflex Coronary Artery Ligation. J. Thoracic Surg. **30:** 57 (July), 1955.

The authors studied the mortality rate in dogs following ligation of the circumflex or the left anterior descending artery and the effect of previous arterialization of the coronary sinus. It was found that after the coronary sinus had been arterialized for 4 to 8 weeks, the mortality rate after left anterior descending artery ligation was 20 per cent as compared with 60 per cent in the control series. However, in those dogs in which the operation had been performed 6 months before, the mortality rate with circumflex coronary arterial ligation was 66 per cent. In this group no significant protection against ventricular fibrillation was afforded by arterialization of the coronary sinus. The loss of protection was accompanied by a retroperfusion of the myocardium, due to marked intimal proliferation and thrombosis within the major venous tributaries of the coronary sinus.

ABRAMSON

Bergstrom, B. L., and Iskwith, I. S.: Myocardial Infarction. Connecticut M. J. **19:** 106 (Feb.), 1955.

The authors review a series of 121 patients with myocardial infarction. A preponderance of this disease was found in men. The over-all mortality rate was 34.7 per cent and the average age was 59 years. The chief problem of treatment lies in making

it early and effective, since no deaths occurred after the second week. The use of anticoagulants in the treatment, and the complications which arise, are discussed. The cases are divided into age groups, showing an increase of mortality in the same ratio as age.

BERNSTEIN

Croft, J. D., and Kearns, J. E.: Radioactive Iodine in the Treatment of Cardiac Disease of the Elderly. Quart. Bull. Northwestern Univ. M. School **29:** 209, 1955.

The thyrocardiac is commonly present and frequently unrecognized among the older age group. Any person with recurrent or persistent tachycardia, atrial fibrillation, or congestive failure who fails to respond to the usual therapeutic measures, no matter what his age or physical status, should be considered thyrotoxic until proved otherwise.

I^{131} is a valuable agent in the diagnosis and treatment of these patients. The authors' results with its use in those cardiac patients who were not hyperthyroid were disappointing insofar as increasing life span was concerned. Symptoms were improved in some.

BERNSTEIN

McLaren, J. A.: Spontaneous Cardiac Rupture Eight Hours Following Myocardial Infarction. Quart. Bull. Northwestern Univ. M. School **29:** 234, 1955.

A case of spontaneous cardiac rupture 8 hours following myocardial infarction is presented. The factors in the etiology, pathogenesis, and pathology of cardiac rupture are discussed.

In every way the case reported is classical. The patient was a woman, there was no previous history of myocardial infarction, and the amount of myocardial fibrosis was slight. Hypertension existed and persisted following infarction. Vomiting was present and in a sense may be construed as an unusual exertion. The anterior descending branch of the left coronary artery was thrombosed, the anterior wall of the left ventricle ruptured, and there was an infiltration of polymorphonuclear cells only at the site of rupture. The case is unusual only in the speed with which rupture occurred following myocardial infarction.

BERNSTEIN

Kaufman, J. M., and Caputo, N. T.: Basilar Rales in Myocardial Infarction. J. A. M. A. **158:** 1521 (Aug.), 1955.

The authors present 4 cases of myocardial infarction in which none of the patients described the usual chest pain but all had midabdominal pain, drop in blood pressure, and left-sided basilar pulmonary rales. Two hundred cases of myocardial infarction were then re-examined, and it was found that 53 per cent had left-sided pulmonary rales, 19 per cent had no rales, 20 per cent showed bilateral rales, and only 8 per cent had unilateral right-sided rales. It is therefore suggested that unilateral left-sided rales are a helpful diagnostic aid in the atypical case of myocardial infarction.

KITCHELL

Prinzmetal, M., and Massumi, R. A.: The Anterior Chest Wall Syndrome—Chest Pain of Cardiac Origin. J. A. M. A. **159:** 177 (Sept.), 1955.

The anterior chest wall syndrome is a complex consisting of somatic involvement of this area leading to pain and tenderness. It is possible that this condition is pathogenetically analogous to the shoulder-hand syndrome and hence possibly of neurovascular origin. Histologic changes are inconsistent. Although the condition occurs very commonly after myocardial infarction, it has been observed in noncardiac individuals and it generally lasts months and even years. If associated with angina pectoris, it can cause persistent pain and can be easily confused with status angiosus. The symptom complex is often misdiagnosed as coronary artery disease and treated accordingly. This error often leads to profound anxiety and depression in the patients and fear and frustration in the physician. The presence of tenderness of the anterior chest wall and absence of signs and symptoms of progressive coronary artery disease are the most important diagnostic features of this symptom complex. Therapeutic tests with corticotrophin, corticosteroids, and x-ray therapy are generally sufficient to uncover the true nature of the pain. Two to 3 days of therapy with corticotrophin or cortisone are often sufficient to bring about much relief of pain, and more prolonged treatment with these agents cures the condition completely as a rule. Roentgen radiation may be substituted for corticoid therapy in 2 to 3 days, and will often clear the condition completely. As the recognition of this common condition is of great importance, it may be advisable that all patients complaining of anterior chest pain (particularly those with the history of myocardial infarction) be examined carefully for the presence of tenderness of the chest wall.

KITCHELL

Mathieu, L., Hadot, E., Vincent, and Hueber: Vaccination against Variola and Acute Coronary Thrombosis. Arch. mal. coeur. **48:** 802, 1955.

During recent mass vaccinations against variola, 8 cases were observed in which myocardial infarction with typical electrocardiographic changes appeared between the seventh and fourteenth day after the inoculation. All were over 53 years of age; 3 had previous angina, and 5 of the 8 died in spite of early treatment. All had an especially large and painful local reaction to vaccination. The coronary thrombosis, which appeared at a time similar to that of post-

vaccination encephalitis, is attributed to a coronary arteritis. It is concluded that vaccination should not be given in the presence of angina, and should be seriously reconsidered in all persons over 50, especially if hypertension or arteriosclerosis is present.

LEPESCHKIN

Carr, C. J., Bell, F. K., Rehak, M. J., and Krantz, J. C.: Effect of Drugs on Myokinase Activity of Coronary Arteries. Proc. Soc. Exper. Biol. & Med. **89:** 184 (June), 1955.

The authors previously reported the presence of a phosphokinase in beef coronary artery homogenates, and a method of estimating this enzymic activity was described. In exploring the mechanism of action of vasodilating drugs, the effect of these agents and other drugs on this enzyme system has been studied. The results indicate that constriction and dilatation of coronary arteries elicited by these vasoactive drugs do not involve the inhibition of the adenylate kinase (myokinase) and adenosine triphosphatase enzyme systems.

MAXWELL

Rogers, F. B.: Unsuspected Cardiac Infarction with Cerebrovascular Accidents. J. Am. Geriatrics Soc. **3:** 714 (Sept.), 1955.

In a review of 134 cases, with a diagnosis of acute cerebrovascular accident or coronary thrombosis, or both, the author found these 2 conditions to coexist in 19 patients (7 per cent). Four case histories were presented in detail. Coexistence of these 2 conditions, each common in the aged, provided an interesting diagnostic problem, since the cardiac lesion may be silent in the presence of a stroke.

RINZLER

Jamison, W. L., DeVera, L., Katakis, G., Alai, J., and Nichols, H. T.: Studies on Coronary Blood Flow with Emphasis on the Treatment of Coronary Insufficiency. Geriatrics **3:** 521 (Aug.), 1955.

This study reports the effects of certain drugs on the coronary flow of mongrel dogs. The blood from the superior and inferior venae cavae was shunted around the right heart, so that the entire outflow of the pulmonary artery represented the coronary venous drainage. Methoxamine hydrochloride (Vasoxyl) produces an effect on the coronary blood flow in proportion to the rise in blood pressure. Norepinephrine produces an increase in coronary flow far in excess of the rise in mean blood pressure. Epinephrine also causes a rise in coronary blood flow. A rise in oxygen content of coronary venous blood after norepinephrine is reported as direct evidence that the oxygen supply of the heart muscle is increased to a greater extent than the oxygen utilization.

RINZLER

Master, A. M., and Jaffe, H. L.: Physiologic Effects of Obesity upon the Heart. The Incidence of Obesity in Coronary Disease. Geriatrics **5:** 299 (May), 1955.

A review of the physiologic effects of obesity upon the heart indicates that obesity reduces work tolerance and cardiac reserve. It increases oxygen consumption, cardiac work, blood pressure, and cardiac rate. Undernutrition lightens the work of the heart. There is a definite increase in the proportion of overweight men with angina pectoris or acute coronary insufficiency, but no statement as to etiologic relationship is possible.

RINZLER

Davis, J. A., and Wiesel, B. H.: The Treatment of Angina Pectoris with a Nitroglycerin Ointment. Am. J. M. Sc. **230:** 259 (Sept.), 1955.

Seventeen patients with angina pectoris were treated with a 2 per cent nitroglycerin ointment in addition to a regimen of rest, long-acting nitrites, sedatives and sublingual nitroglycerin. The effects of the ointment were judged by the subjective response of the patient and by the reduction in the number of sublingual tablets required. Nine of the patients were classified as greatly helped, 4 were improved but had no decrease in the number of attacks, and 4 were unaffected by the treatment

These results suggest that nitroglycerin ointment may be a useful adjunct in the management of coronary insufficiency. The principle of slower absorption, with prolonged vasodilation of the coronary arteries, deserves further clinical trial. Sudden withdrawal of this ointment may produce more severe coronary insufficiency..

SHUMAN

Rosenberg, H. N., and Michelson, A. L.: The Use of Pentaerythritol Tetranitrate in Chronic Coronary Insufficiency. Am. J. M. Sc. **230:** 254 (Sept.), 1955.

The effect of Peritrate upon the severity of cardiac pain, was studied in 20 patients over a period of six months by the double-blind technic. The patients kept a daily score card to record the severity of pain and the number of nitroglycerin tablets used. No side effects were noted with doses of 20 mg., 4 times a day; on 30 mg., 4 times daily, 2 patients experienced drowsiness and 3 became nauseated. Five patients showed statistically significant improvement and 16 did not. A lag of 3 to 7 days in therapeutic action was observed in 50 per cent of the patients, and a carry-over effect after omission for 1 or 2 days was noted.

It is concluded that Peritrate is of value in the treatment of approximately 25 per cent of patients with coronary insufficiency.

SHUMAN

Gammill, J. F., Applegarth, J. J., Reed, C. E., Fernald, J. D., and Antenucci, A. J.: Hemodynamic Changes Following Acute Myocardial Infarction Using the Dye Injection Method for Cardiac Output Determination. Ann. Int. Med. **43:** 100 (July), 1955.

Cardiac output was determined 96 times in 39 patients with acute myocardial infarction by the dye-dilution technic. An extensive review of the clinical records and electrocardiograms was made in an effort to find measurements or observations that would correlate with the level of cardiac output and stroke volume. It was found that patients who had sustained the most marked fall in pulse pressure, or in mean blood pressure, or had been in pulmonary edema, showed the lowest average values for cardiac output and stroke volume. Low values were also observed in patients with a moderate fall in pressure if they also showed certain other signs of impaired cardiac function, *i.e.*, bilateral pulmonary congestion and a diastolic gallop, or a tachycardia greater than 108 per minute after bedrest. Many of the patients who were hospitalized and placed at bedrest soon after the onset of an acute myocardial infarction maintained their circulation at normal, basal levels. This was true even for several of the patients who had sustained an appreciable drop in mean blood pressure or pulse pressure. Those patients who survived despite very low levels of cardiac output and stroke volume initially, showed an increase in cardiac output and stroke volume when studied approximately 4 weeks later. A significant decrease in mean blood pressure, total peripheral resistance, and venous pressure was observed after 4 weeks of hospitalization. Changes observed in venous pressure, mean circulation time, and system volume during hospitalization, indicate that cardiac failure was present at the time of the initial study, even though the cardiac output was not significantly reduced.

WENDKOS

CONGESTIVE HEART FAILURE

Hamilton, M., Barnett, A. J., and Lowe, T. E.: Ischaemic Episodes in Cardiac Failure: Acute Arterial Insufficiency with and without Structural Blockage. M. J. Australia **2:** 93 (July), 1955.

Clinical histories are presented of patients suffering from congestive cardiac failure who developed peripheral ischemia, some with, and others without, any demonstrable arterial occlusion. The mechanism of ischemia in the absence of arterial occlusion is discussed.

The authors conclude that in vessels having active tension, for a given pressure there is a tension above which the vessel must close; conversely, for a given tension, there is a pressure below which the vessel must close. If, with a normal pressure, the active tension should rise to a sufficient degree, the vessel will close (spasm). This may be the mechanism of closure of vessels subject to direct irritation. If with a normal active tension the pressure is lowered, the vessel will also close, as may occur below the site of an embolus. In the patients with advanced cardiac failure there was presumably high tension in the vessel wall, due to strong sympathetic activity attempting to maintain the homeostasis of the blood pressure in face of a low cardiac output. Thus the stage was set for critical closure.

BERNSTEIN

Hejtmancik, M. R., and Herrmann, G. R.: Refractory Congestive Heart Failure in the Elderly Patient. Texas J. Med. **51:** 238 (May), 1955.

Refractory congestive heart failure is managed similarly in all age groups, but in the elderly, coronary atheromatosis is a more frequent etiologic factor. Proper therapy of precipitating, contributing, and perpetuating causes is essential in the refractory patient with congestive heart failure.

A review of the therapeutic regimen may bring about changes with gratifying results. Proper attention must be paid to the restriction of sodium, limitation of activity, adequate digitalization, and optimum use of diuretics. The geriatric patient is more susceptible to electrolyte complications than the young patient. Adequate electrolyte studies are necessary in the refractory case, although determinations of hydrogen ion concentration and chloride in the urine may be of much value. Proper correction of serum electrolytes may again make the failure responsive.

BERNSTEIN

Davis, J. O., Howell, D. S., Hyatt, R. E., and Casper, A.: Effects of Acute and Chronic Digoxin Administration in Dogs with Right-Sided Congestive Heart Failure Produced by Pulmonary Artery Constriction. Circulation Research **3:** 259 (May), 1955.

The acute and chronic effects of digoxin on cardiovascular and renal hemodynamic function and sodium excretion have been studied in 7 dogs with right heart failure produced by pulmonary artery constriction.

Digoxin administration in 7 dogs brought about a fall in right atrial pressure in every instance, and an increase in cardiac output of 11 to 70 per cent in 5 of the 7 animals. Total peripheral resistance was reduced in the 5 animals showing increased cardiac output. Right ventricular systolic pressure increased in all. A striking increase in renal sodium excretion occurred in 4 of the 7 animals, and an increase in glomerular filtration rate and renal plasma flow resulted in every dog. Glomerular filtration rate increased from 50 to 63 ml./min.; whereas renal plasma flow increased from 111 to 151 ml./min. (mean values for 2 dogs).

With chronic digoxin administration, improvement in cardiovascular and renal hemodynamic

function and sodium excretion began after 7 days of digoxin therapy. The data suggest an effect on the right ventricular myocardium and provide evidence of myocardial depression in dogs with pulmonary artery constriction.

MAXWELL

Howell, D. S., Davis, J. O., and Laquer, G. L.: Effect of Hypophysectomy on Electrolyte Excretion in Dogs with Ascites Produced by Thoracic Inferior Vena Cava Constriction. Circulation Research **3:** 264 (May), 1955.

The effect of hypophysectomy on ascites formation has been studied in dogs with constriction of the thoracic inferior vena cava. In animals in which hypophysectomy was complete or nearly complete, sodium excretion increased strikingly from the previous low level. The abnormally low ratio of fecal sodium and potassium excretion increased in all dogs. Changes in electrolyte excretion were accompanied by decreases in femoral venous pressure (except in 2 dogs in which hypophysectomy was incomplete), cardiac output, glomerular filtration rate, and renal plasma flow. Replacement therapy with ACTH was without effect on electrolyte excretion, femoral venous pressure, and cardiac output, but glomerular filtration rate and renal plasma flow returned toward, or to, control levels, and an eosinopenia resulted. Both growth hormone and thyroid stimulating hormone produced an elevation in femoral venous pressure and a concurrent drop in renal sodium excretion; discontinuation of these hormones was followed by a fall in femoral venous pressure and the reappearance of a negative sodium balance. Reconstriction of the thoracic inferior vena cava and return of venous pressure to the high prehypophysectomy level was followed by marked sodium retention again. It is concluded that pituitary hormones contribute to the maintenance of an adequate level of venous hypertension which is essential for ascites formation.

MAXWELL

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

Itatsu, H.: Theoretical Interpretation of Contiguous Bipolar ECG and Its Relationship to the Time of Arrival of Activation. Part II. Application to Precordial Lead Electrocardiogram. Jap. Circ. J. **19:** 230 (Aug.), 1955.

The peak of the main deflection of contiguous bipolar lead electrocardiograms was employed as the point indicating the time of arrival of activation. In 10 normal subjects and 6 abnormal subjects with left ventricular hypertrophy or with incomplete right bundle branch block, the intervals between the beginning of QRS duration in precordial leads and the time of arrival of activation were measured. In incomplete right bundle branch block, the appropriateness of preferring either first nadir or second nadir as the point indicating the time of arrival of activation was discussed, but further study on this problem seemed to be necessary. The intervals between the beginning of QRS duration and the time of arrival of activation in the precordial leads of normal subjects were quite similar to those previously reported by other investigators. These intervals in abnormal subjects with left ventricular hypertrophy were longer than in normal subjects, but the activation process in the hypertrophied ventricle was almost similar to that in normal subjects, except that the time of arrival of activation at the subepicardial surface of the hypertrophied ventricle is generally later than in the normal one.

BERNSTEIN

Mori, M.: Atrioventricular Connecting System of Crocodile Heart. Kyushu Memoirs Med. Sc. **5:** 199 (Mar.), 1955.

The atrium and ventricle of the crocodile heart is connected by 4 kinds of connecting systems. The connecting system in the interventricular septum is the precursor of the principal connecting system of the bird and the conducting system of mammalia. This system is also a derivative of the funnel-plate. With the development of the interventricular septum, a part of the funnel-plate is brought into it and becomes the principal connecting system.

BERNSTEIN

Rosa, L., and Kunos, I.: The Role of the Low-Frequency Phonocardiogram in the Evaluation of Mitral Valvulotomy. Ztschr. Kreislaufforsch. **44:** 689, 1955.

The phonocardiogram, registered with an electrodynamic microphone without filters ("accelerogram"), showed a more or less complete return to normal in 75 per cent of 230 operated cases of mitral disease. The duration of the first systolic group of vibrations, which corresponds to the isometric phase of contraction, and that of the second group, which is held to correspond to maximal ejection, decrease after successful valvulotomy, as does to distance from beginning of the second heart sound to the opening snap of the mitral valve. The third systolic group shows an increased duration, which is attributed to increased stroke volume. The duration and the frequency of the third heart sound was found to decrease.

LEPESCHKIN

Frank, E.: Absolute Quantitative Comparison of Instantaneous QRS Potentials on a Normal Subject with Dipole Potentials on a Homogeneous Torso Model. Circulation Research **3:** 243 (May), 1955.

Results of a critical experiment for indirect quantitative determination of influence of human-body inhomogeneity and applicability of fixed-location

dipole hypothesis for the QRS complex are presented in terms of absolute boundary equipotentials at 3 different instants of the QRS complex of a normal male subject and for a fixed-location dipole immersed in an accurate 3-dimensional homogeneous torso model of the same subject. It is concluded that the fixed-location dipole representation accounts for approximately 95 per cent of the QRS complex at any body surface point and that influence of inhomogeneities on surface potentials accounts for fluctuations estimated to be roughly plus or minus 10 per cent. Steep potential gradients at the left shoulder give evidence of complexity of left arm potentials as compared with other limbs.

MAXWELL

Pipberger, H., Kälin, R., and Rossier, P. H.: Vectorcardiographic Investigations in Hypertensives During Pressure Reduction by Hexamethonium. Cardiologia **27:** 166 (Fasc. 3), 1955.

In 13 hypertensive patients a marked drop in blood pressure was achieved by intravenous administration of hexamethonium. Vectorcardiograms were recorded before and after the reduction of pressure, and changes in the spatial orientation of QRS and T were determined. While both QRS and T loops showed considerable alterations in their direction, the changes in their angle were insignificant and the direction of the spatial ventricular gradient remained remarkably constant. The results of these studies cast doubt on the view that the ventricular gradient is to be ascribed to pressure effects upon the subendocardial layers of the ventricular myocardium.

PICK

Dick, H. L. H., and McCawley, E. L.: A Comparison Study of Drugs in Experimental and Clinical Auricular Fibrillation. Am. Heart J. **50:** 442 (Sept.), 1955.

Each of the 4 basic theories for the genesis of atrial fibrillation and flutter is supported by experimental procedures using laboratory animals: (1) circus movement, (2) re-entry theory, (3) multiple ectopic focus and (4) single ectopic focus theory. The authors found that drugs with high experimental antifibrillatory potency did not necessarily exhibit therapeutic action when subjected to clinical test.

Hypervagotonia is undoubtedly an important factor in the initiation of atrial fibrillation, but not in the maintenance of the arrhythmia. Unknown factors appear to be responsible for its maintenance.

Diphenhydramine hydrochloride (Benadryl) may be added to the list of successful therapeutic agents for clinical atrial fibrillation. Although our results do not indicate its routine substitution for quinidine, it may prove valuable in selected patients. Banthine may prolong the myocardial refractory period and prevent or reverse atrial fibrillation in experimental animals, but it was not useful in human beings.

RINZLER

Gross, H., Kepes, E. R., Young, D., and Enselberg, C. D.: Electrocardiographic Changes During Mitral Commissurotomy. Am. Heart J. **50:** 373 (Sept.), 1955.

Continuous electrocardiographic observations were made on 100 patients undergoing mitral commissurotomy. Changes occurred in every case, and included practically every known abnormality of rate and rhythm, as well as variations in form and amplitude of atrial and ventricular defections. The most frequently encountered serious arrhythmia was ventricular tachycardia (44 cases), usually irregular and associated with occlusion of the mitral orifice by the surgeon's finger. In three fourths of the cases it was unnecessary to use any drugs; indeed, only half the cases of ventricular tachycardia were treated. The best response to drug therapy resulted from the use of vasopressor agents. No constant causal relationship was found between blood pressure or oximetric determinations and RS-T deviations.

RINZLER

Pines, I.: The Origin of the Initial Negative Deflection in the Right Auricular Endoelectrogram. Am. Heart J. **50:** 391 (Sept.), 1955.

The experiments in this report were carried out on 4 horses, 1 mule, 43 young bulls, and 10 dogs. Various characteristics inherent to the inscription of the negative initial deflection in the right atrial endoelectrogram were studied. It was estimated that judging by the length of the atrioventricular conduction, the Q_a wave starts simultaneously with the totally negative atrial deflection, which is typical for the sites adjacent to the S-A node, and precedes the so-called "O" wave of the electrocardiograms of equines.

In this investigation, the Q_a wave was found only in the upper parts of the right atrium. It seemed to be a purely right atrial phenomenon, because it did not precede the left atrial complex in the right atrial endoelectrogram.

Drugs inducing bradycardia and slowing the conduction of the stimuli caused, first, changes of amplitude of the Q_a wave, then an increase of its duration, and later its complete separation from the main atrial complex.

The Q_a wave was believed to be the result of uneven distribution of vectors of electric forces during the initiation of the stimulus by the S-A node and the preponderance of the negative forces in certain parts. This was thought to be the result of the nonspherical shape and the irregularity of structure of the S-A node.

RINZLER

Braun, H. A., Surawicz, B., and Bellet, S.: T Waves in Hyperpotassemia. Their Differentiation from Simulating T Waves in Other Conditions. Am. J. M. Sc. **230:** 147 (Aug.), 1955.

T waves in hyperpotassemia and in normopotassemic subjects were compared in three groups: 100 normal individuals; patients with hyperpotassemia due to renal disease; and patients free of electrolyte disturbances with "simulating" T waves. The T wave and components of the QT interval were measured in each electrocardiogram. Mathematical expressions were listed for height, width, symmetry, steepness, pointedness, and slimness of the T-wave features, in an attempt to compare the findings in hyperpotassemia with the simulating T waves not associated with electrolyte imbalance. Blood sodium and potassium were determined simultaneously with electrocardiograms. The differentiation of the tall T waves in these groups proved extremely difficult. Steepness, pointedness, and tallness were of no diagnostic significance. Narrowness of the T wave was the only feature of possible significance; this was related to the later onset of the T deflection in hyperpotassemia. Symmetry was difficult to evaluate, since the point of onset of the T wave may be obscure. Pre-existing T-wave abnormalities commonly caused difficulty by masking the hyperpotassemic effects. A terminal slur in QRS or an S wave in lead 1 or V_6, without gross widening, were frequent findings in hyperpotassemic records; they may prove helpful in evaluating the T-wave changes. By studies in dogs after infusion of potassium salts, it was confirmed that T-wave changes in hyperpotassemia are primary and not secondary to QRS changes.

SHUMAN

Bussan, R., Torin, S., and Scherf, D.: Retrograde Conduction of Ventricular Extrasystoles to the Atria. Am. J. M. Sc. **230:** 293 (Sept.), 1955.

A group of 35 patients, whose electrocardiograms exhibited sinus rhythm with ventricular extrasystoles, was studied by means of an esophageal lead, and a simultaneously recorded lead II, in an effort to demonstrate retrograde conduction of ventricular systoles to atria. The criteria used for the determination of retrograde conduction were (1) the p′ waves may be different in contour from the sinus P wave, (2) the p′ wave may be premature, and (3) the presence of fusion P waves. The most significant criterion was the prematurity of p′ wave. In 25 of these patients a sinus tachycardia prevented the determination of the presence of retrograde conduction. The latter phenomenon was found in 8 of 9 patients with ventricular extrasystoles and a slow sinus rhythm. There is apparently less likelihood of retrograde conduction at a rapid rate; however, at a rate of 80 per minute, or lower, most of the ventricular extrasystoles will be retrograde-conducted to the atria.

SHUMAN

HYPERTENSION

Newborg, B., and Kempner, W.: Analysis of 177 Cases of Hypertensive Vascular Disease with Papilledema. One Hundred Twenty-six Patients Treated with Rice Diet. Am. J. Med. **19:** 33 (July), 1955.

The 2 most important factors influencing the effectiveness of the rice diet in the treatment of malignant hypertension are the renal status (especially since salt-losing often precludes the use of diet in patients with advanced renal involvement) and the length of time the patient is willing to adhere strictly to treatment. The urinary excretion of chloride, calculated as sodium chloride, on the basic rice diet should ordinarily be 5 to 15 mg. per 100 ml. of urine; on the "modified" rice diet, it should be 15 to 25 mg.

In 33 patients with hypertensive neuroretinopathy on the rice diet, electrolyte imbalance developed within the first 3 months. Treatment with drastic salt restriction could not be carried out. In 31 of these 33 patients, the total phenolsulfonephthalein excretion in 2 hours was below 36 per cent. All 33 patients died. In the other patients who adhered strictly to the dietary regimen, the malignant hypertension improved with an increase in survival time, at least in those who did not have significant renal impairment and did not lose significant quantities of sodium in the urine. In 92 of 100 patients in whom eyeground photographs were available, papilledema disappeared completely. Intensive dietary treatment is recommended as early as possible and should be continued until all signs of the vascular disease have disappeared.

HARRIS

Choremis, C., Tsenghi, C., and Economou-Mavrou, C.: Does Measles Cause Hypertension? Arch. Dis. Childhood **30:** 264 (June), 1955.

In 62 patients with measles, between 3 and 13 years of age, the systolic blood pressure under a standard set of conditions increased. In 140 normal controls under the same set of standard conditions, systolic hypertension was not observed. The authors believe that the virus infection causes either edema and hyperfunction of the adrenal cortex or a stimulation of the anterior lobe of the pituitary gland.

HARVEY

Braun-Menendez, E.: The Role of Renotrophine in Experimental Hypertension of Renal Origin. Acta cardiol. **10:** 324 (Fasc. 4), 1955.

The author develops his present views concerning the genesis of renal hypertension. A hypothetical substance develops in the organism under the influence of protein-rich diet in the presence of normal function of the thyroid gland and of the anterior pituitary lobe. This substance, called renotrophine, enhances the growth of renal tissue and is metabo-

ized by it. If renal hypertrophy is hindered, the concentration of renotrophine in the blood rises and leads to arterial hypertension. The pressor substance is either renotrophine itself or renin, released by the kidneys under the influence of excess renotrophine.

In support of this working hypothesis the results of 4 types of experiments are quoted: (a) hypophysectomy or thyroidectomy in hypertensive rats lowers the blood pressure and this can be attributed to less production of renotrophine, (b) treatment with thyroid and pituitary extracts of rats with reduced renal tissue reveals their latent hypertension, (c) increase of functional renal tissue induced by parabiosis in hypertensive rats lowers the blood pressure, and (d) reduction of functioning renal tissue sensitizes animals to the nephrosclerosing action of certain compounds such as desoxycorticosterone.

PICK

Denny, J. L., Frasher, W. G., and Hoytt, D. D.: Clinical Evaluation of Drug Therapy in Hypertension. Am. J. M. Sc. **230:** 169 (Aug.), 1955.

Following an initial period of evaluation, 130 patients from the hypertensive clinic received placebo therapy and treatment with reserpine, hydralazine, hexamethonium, and combinations of these hypotensive agents. Pressure was recorded by averaging the systolic and diastolic pressures over the total time in a single course rather than selecting isolated low pressures. Paired values were reported, using the placebo-control period of each patient for comparison with the treatment period. In this way, a statistically significant difference was demonstrated between placebo and each therapeutic regimen. The combined therapy (hexamethonium-hydralazine) appeared more effective than the other groups. Side-effects were observed during each treatment schedule, including 29 per cent of those receiving the placebo. Specific cases are cited in which excellent pressure reductions occurred on each of the plans of therapy. These good results could not be predicted, nor did a significant lowering of pressure ensue in the majority. The authors stress the essentially experimental and empiric nature of drug therapy in hypertension.

SHUMAN

Winsor, T.: The Comparative Effects of Four Ganglionic Blocking Agents on the Cardiovascular System of Man. Am. J. M. Sc. **230:** 133 (Aug.), 1955.

The relative hypotensive effects of 4 ganglionic blocking agents, SU3088, Azamethonium, SE1950, and hexamethonium, were measured in 59 patients with moderately severe, uncomplicated hypertension. Control pressure was recorded as the lowest value reached over a 3-month period. Pulse rates, postural blood pressures, and cold pressor reactions were recorded before and during treatment periods.

SU3088 produced the greatest hypotensive effect in smallest dosage. Approximately 200 mg. caused hypotension within 24 hours, owing to rapid absorption on oral administration. Blood pressure reduction and slight tachycardia were noted within 2 hours after a single dose. Postural hypotension was reduced by giving reserpine with this agent. SU3088 apparently blocks all autonomic ganglia, both sympathetic and parasympathetic. In 2 patients with causalgia, there was diminished sweating, relief of pain, increased mobility of the parts, and increases in skin temperatures. The most annoying side-effect was that of visual blurring, which proved advantageous in the regulation of dosage.

The other agents tested; namely, hexamethonium, SC1950, and Azamethonium, were less effective and produced less hypotensive effect as larger doses were employed.

SHUMAN

Sapeika, N.: The Adrenal Cortex and Hypertensive Disease. Arch. Int. Med. **96:** 654 (Nov.), 1955.

Essential hypertension can still be viewed as nonrenal in origin. Adrenal cortex hormones are essential for the overt manifestation of such diseases as hypertension, diabetes mellitus, and prostatic cancer, but the exact role of the adrenal cortex in essential hypertension remains to be established. The complicated nature of the subject is well shown by the varied opinions expressed.

Since adrenal cortical hormones maintain the normal arterial tone and the sensitivity of these vessels to adrenergic hormones, hypertension may develop in man on the basis of hormonal sensitization of peripheral vessels to sympathetic action. The adrenal cortex is more fundamentally concerned in the maintenance of hypertension than is the sympathetic nervous system. Further observation will be required to establish whether some type of sympathectomy and adrenalectomy is better than adrenalectomy alone. If such surgical treatment proves successful, the eventual treatment of hypertension with drugs becomes more likely, since it points toward the medical control of the sympathetic nervous system activity and the depression of adrenal cortex function.

By the use of suitable drugs acting on the anterior pituitary gland or directly on the adrenal cortex (chemical hypophysectomy or chemical adrenalectomy) the elevated blood pressure and other features of hypertensive disease may be restored to normal. Suitable agents are available to maintain the patient, should adrenal insufficiency be produced.

BERNSTEIN

Uchigasaki, S.: On the Heredity of Essential Hypertension. Tohoku J. Exper. Med. **61:** 245 (Feb.), 1955.

In Japan, about 60 per cent of hypertensive

persons die of apoplexy. Among the inhabitants of the agrarian villages situated in the basin of the River Omono, 80 per cent of them have records of cases of cerebral hemorrhage among their ancestors, while of the inhabitants in some fishing villages, only 40 per cent had such genealogic records. In the former district, nonhereditaries counted only 10 to 20 per cent among the hypertensive, but in the latter district, 20 to 60 per cent of the hypertensive claimed nonheredity. The reason for this discrepancy seems to lie in the fact that the environmental conditions are incomparably more conducive to longevity and prevention of cerebral hemorrhage in the latter, so that the deaths, even in hypertensive individuals, have been attributed to simple senility, and the hereditary tendency for hypertension remained concealed.

Various investigations have proved the prevalence of hereditary predisposition, even among the younger generations, who have not yet suffered much from unhealthy environmental conditions. Essential hypertension shows a considerable heredity that seems to be dominant in character. The environmental conditions over a long period apparently play such an important role, however, that the author hesitates to conclude essential hypertension to be a hereditary disease.

BERNSTEIN

Wilhelmj, C. M., Gunderson, D. E., Shuput, D., and McCarthy, H. H.: The Effect of Diet on the Blood Pressure and Heart Rate of Normal Dogs. Animal Fat. Am. J. Digest. Dis. **22:** 219 (Aug.), 1955.

Dogs were subjected to repeated prolonged fasts and realimentation with diets containing 50 per cent or more of the calories from beef suet or butter (fat episodes). This was repeated 6 times during a period of 2 years. As a result of this procedure, the following changes gradually developed in each of 4 dogs. In response to fasting the normal fall of blood pressure was replaced either by a failure to fall or by a progressive rise to high levels. The heart rate was not significantly different from that in fasts in which the blood pressure showed the usual fall. If the animals were receiving an optimal nonstress diet after the fat episodes the blood pressure would remain at the control level for 50 days or more, but the abnormality was dormant and would appear as soon as the stress of fasting started. The blood pressure while on the high-fat diet was not predictable; usually it was normal or low, less often, higher than normal.

After several fat episodes, the blood pressure was abnormally high on a balanced high-calorie diet. Several fat episodes sensitized the blood pressure response to high-calorie diets more than a preliminary fast. Paralleling the above changes, the animals developed a very pronounced and persistent eosinopenia. Three of the dogs sensitized by several fat episodes were subjected to the stress of muscular work (treadmill) or to cold, but the blood pressure responses were not exaggerated. It is suggested that sensitization by several fat episodes may render an an animal potentially hypertensive as disclosed in abnormal responses to the metabolic stresses of fasting and high-calorie diets.

BERNSTEIN

Baldrighi, V., and Ferrari, V.: Systemic and Pulmonary Pressor Response to Serotonin (5 Hydroxytryptamine) in Man. Folia Cardiol. **14:** 7 (Feb.), 1955.

The effect of a slow infusion or of a rapid intravenous injection of serotonin on blood pressure was studied in 34 subjects. In 4 patients with hypertension and in 5 normal subjects the pressures in the right atrium and in the pulmonary artery were measured. An increase in venous, right atrial and pulmonary artery pressure preceded the decrease of pressure in the femoral and retinal arteries. The heart rate and the stroke volume were increased in most cases; the stroke volume was measured by the sphygmographic method. These circulatory changes were better related to the velocity of injection than to the total dose of serotonin injected. It was concluded that the primary effect of serotonin probably is an increase in pulmonary pressure. The possibility of an acute liberation of serotonin as a factor in the circulatory changes in pulmonary embolism and in coronary thrombosis is briefly discussed.

CALABRESI

Friedman, S. M., Hinke, J. A. M., and Hardwick, D. F.: Sodium Tolerance in Experimental Hypertension. Circulation Research **3:** 297 (May), 1955.

A simple sodium tolerance test for the rat was prepared and standardized to test the postulate that in experimental hypertension a sodium imbalance might be masked by a new homeostasis.

This standard sodium tolerance test was applied to rats subjected to renal compression, to DCA treatment and to compound F acetate treatment. The first procedure is known to produce renal hypertension without overt evidence of sodium imbalance. DCA and compound F treatments were selected to represent hormonal hypertension with and without overt sodium imbalance.

A definite distortion in the sodium tolerance curve occurred following all 3 treatments. The change, common to all, was in the direction of an accelerated excretion of the imposed load, even though no change in plasma sodium level was observed.

The degree of distortion in sodium tolerance was proportional to the blood pressure level. It also occurred, however, in treated rats whose pressures remained normotensive. The working hypothesis is made that the sodium imbalance is requisite to the blood pressure elevation but that an equilibrium may be attained without necessarily involving the blood pressure.

MAXWELL

Freis, E.: Treatment of the Elderly Hypertensive Patient. J. Am. Geriatrics Soc. **3:** 710 (Sept.), 1955.

The intensive treatment of hypertension is seldom indicated in the geriatric patient. Drugs of choice for the elderly patient with diastolic hypertension are rauwolfia, veratrum and hydralazine. The ganglion-blocking agents should be avoided in patients beyond the age of 70 years. Most elderly patients, particularly those with primarily systolic hypertension, require no special treatment.

RINZLER

Mader, I. J., Iseri, L. T.: The Effect of Oral 1-Hydrazinophthalazine Therapy on Renal Function in Essential Vascular Hypertension. Am. Heart J. **50:** 556 (Oct.), 1955.

The authors report their results of controlled studies of 14 patients with severe essential hypertension. Patients were placed on a therapeutic regimen for 2 to 6 weeks. They received from 400 to 600 mg. of oral hydrazinophthalazine per day in conjunction with 20 to 100 mg. of hexamethonium subcutaneously per day, administered in divided doses. An effective fall in mean blood pressure was recorded in 12 patients, and in 10 patients a significant increase in renal plasma flow was noted. Improvement in renal blood flow occurred without increase in cardiac output, thus indicating a decrease in renal ischemia.

RINZLER

Miller, A. J., Cheng, T. O., and Freedman, M. E.: Electrocardiographic Changes during Norepinephrine-Induced Hypertension in Normal Man. Am. Heart J. **50:** 567 (Oct.), 1955.

The electrocardiographic alterations occurring in 9 normal men during norepinephrine-induced hypertension, before and after administration of atropine sulfate, are reported. These changes include: abnormal S-T segment or T-wave changes in leads reflecting the left ventricle, decrease in height or inversion of T waves in right-sided chest leads, increase or decrease in height of T waves in left-sided precordial leads, and increase in height of R waves in one or more of the left-sided precordial leads.

The authors list the following possible mechanisms for these electrocardiographic changes: (1) direct effects of norepinephrine on the myocardium, thereby directly affecting depolarization or repolarization; (2) effects of reflex vagal stimulation on the electric activity of the heart; (3) alterations in configuration secondary to changes in heart rate; (4) changes due to altered position of the heart; (5) changes in depolarization and repolarization due to the induced systemic and pulmonary hypertension; and (6) electrocardiographic changes secondary to emotional disturbance, due in turn to the side-effects of norepinephrine and atropine sulfate.

Side reactions included headache, chest constriction, palpitation, and cold sweating. Arrhythmias were induced that included sinus bradycardia, sinus arrhythmia, A-V dissociation, and wandering pacemaker.

RINZLER

PATHOLOGY

Dick, M. M.: Aneurysms of the Posterior Ventricular Wall. South. Med. J. **48:** 465 (May), 1955.

The author presents 4 cases of aneurysm of the posterior wall of the left ventricle, diagnosed antemortem. In 1 instance the electrocardiogram showed persistent and marked S-T-segment depressions in the reciprocal chest leads, which were considered to have the same significance as S-T-segment elevations would have in the direct leads. However, the diagnosis of a posterior wall aneurysm was actually made on fluoroscopic examination at which time a definite systolic bulge in the midzone of the inflow tract was seen. Confirmation of the clinical impression was obtained at postmortem examination. Two other cases demonstrated signs of posterior wall aneurysm by fluoroscopy, while in the case of the fourth patient this procedure was not performed.

The author pointed out that the most common finding in the electrocardiogram of a posterior wall aneurysm is persistent S-T-segment elevations in leads 2, 3 and aVF, with deep, wide Q waves. Less frequently, persistent S-T-segment depressions in the chest leads are noted. Intraventricular block is often present. However, a posterior wall lesion may exist without any of the characteristic findings. The aneurysm can be demonstrated fluoroscopically in the left anterior oblique view by a systolic bulge or by quiet pulsations in the aneurysmal zone.

ABRAMSON

Halter, B. L.: Non-penetrating Trauma to the Heart. Am. J. Surg. **90:** 237 (Aug.), 1955.

The author reviewed the subject of nonpenetrating trauma to the heart. This can occur as a result of direct contusion against the chest wall or spine or from a tearing force due to the suspensory nature of the heart. Concussion, producing multiple minute hemorrhages or vagosympathetic responses, and pressure changes within the heart following compression of distant parts are also etiologic agents. Other factors are hemorrhage into atheromatous plaques reducing the lumen of a previously involved coronary blood vessel and secondary alterations from shock, hemorrhage, and stress.

The major symptoms and physical signs of moderate to severe cardiac trauma are unconsciousness, cardiac arrhythmias, tachycardia, chest pain, cyanosis, friction rub, tamponade, dyspnea, angina pectoris, and myocardial insufficiency.

Treatment depends upon the nature of the lesion. In the case of contusion or bruising of the heart, essentially the same measures as those used for myocardial infarction are instituted. Tamponade requires aspiration or surgical drainage. Rupture of

the myocardium may respond to immediate surgical repair.

ABRAMSON

Holman, E., and Peniston, W.: Hydrodynamic Factors in the Production of Aneurysms. Am. J. Surg. **90:** 200 (Aug.), 1955.

The authors investigated the various factors that may be responsible for the formation of poststenotic dilatation of the aorta, using a series of puppies. Several different methods were used in producing the lesion.

The authors believed that the hydraulic laws that govern the flow of fluid through an expansile elastic tube are of prime importance in development of the poststenotic dilatation. In the pulsating flow of blood a momentary retardation in movement occurs during diastole, and it is accentuated just beyond a stenosis. During systole a stream of blood emerges from the stenotic channel at a greatly increased velocity as compared with the velocity in the broader channel either proximal or distal to the narrowing. The fact that the rapidly ejected stream runs into the more slowly flowing poststenotic stream causes a sudden arrest in its forward flow. As a result, the high kinetic energy of the swiftly moving stream is suddenly converted into high potential energy or lateral pressure that may be responsible for the dilatation. The clash of the 2 streams of differing velocities also produces eddies of turbulent and reversed flow and the formation of shocks or impacts of alternating high and low pressure. The impacts against the elastic wall may result eventually in its distension. A third factor producing dilatation is lowered velocity due to the widening of the stream diameter resulting from the first 2 mechanisms. Finally, the various hydraulic stresses imposed upon the vessel wall by stenosis elicit the phenomenon of structural fatigue and eventually distension of the yielding elastic wall.

ABRAMSON

Barr, J. F.: The Use of Pericardial Biopsy in Establishing Etiologic Diagnosis in Acute Pericarditis. Arch. Int. Med. **96:** 693 (Nov.), 1955.

A case of acute tuberculous pericarditis is reported that presented great difficulty in etiologic diagnosis. Diagnosis was established after pericardial biopsy. Though negative bacteriologic examination was not an unusual feature, the response to appropriate antituberculous therapy and reversal of the P.P.D. test are considered adequate evidence for tuberculosis infection. This patient has maintained a satisfactory clinical response on the presently accepted treatment.

BERNSTEIN

Butler, T. C.: A Case of "Toxic Myocarditis" Due to the Common Cold with an Unusual Type of Electrocardiogram. M. J. Australia **1:** 764 (May), 1955.

The author reports a case of myocarditis, proved at autopsy to be secondary to an upper respiratory tract infection, with accompanying cough of a severe prolonged character. The electrocardiogram was of interest in that it showed a sinoatrial block with an atrioventricular nodal rhythm, as well as many ventricular extrasystoles, mostly as coupled beats with a fixed interval and from a single focus. The QRS complex showed aberrant conduction. On the eighth day of her illness, her second day of hospitalization, the patient suddenly died.

BERNSTEIN

Freeman, Z.: A Case of Fiedler's Myocarditis Simulating Pericardial Effusion. M. J. Australia **1:** 273 (Feb.), 1955.

A male patient, aged 36 years, was observed over a period of 3 weeks, gradually deteriorating, with a progressive myocardial lesion of unknown etiology and with a minimal amount of subjective complaint, despite much venous congestion. This case shows that the classical signs of pericardial effusion can be simulated by gross dilatation of the heart with equal damage to both sides. Even pulsus paradoxus was quite pronounced in this case. The only accurate method of solving the problem was cardiac catheterization, which is the case of cardiac dilatation clearly shows the catheter in the right atrium against the extreme outline of the heart. At postmortem examination the findings were those of Fiedler's myocarditis.

BERNSTEIN

Caplan, H.: Monilial (Candida) Endocarditis Following Treatment with Antibiotics. Lancet **2:** 957 (Nov. 5), 1955.

A 43-year-old man had a stormy course after partial gastrectomy for duodenal ulcer. During hospitalization from August to December, 1954, he received large doses of penicillin, streptomycin and aureomycin. On April 19, 1955, there was an embolus to the left leg and on May 6 to the right external iliac artery. The patient died May 15, 1955, following a cerebral embolus. Fever was never an impressive feature.

Autopsy revealed stenosis of the mitral valve and polypoid vegetations on the atrial aspect of the anterior cusp. These vegetations and the clots in peripheral arteries were found to contain fungi. Cultures for fungi were not made so that the diagnosis of Candida endocarditis is only a strong presumption. The relation to heavy administration of antibiotics is stressed.

MCKUSICK

PATHOLOGICAL PHYSIOLOGY

Baratz, R. A., and Ingraham, R. C.: Capillary Permeability during Hemorrhagic Shock in the Rat. Proc. Soc. Exper. Biol. & Med. **89:** 642 (Aug.–Sept.), 1955.

There is no difference in the disappearance

curves of bovine albumin conjugate from the vascular tree of control rats or those surviving or succumbing to the hemorrhagic shock. This evidence seems to indicate that an increase in capillary permeability is not a major factor in the transition from the reversible to the irreversible phase of hemorrhagic shock. Whatever the sequence of events that lead to the ultimate development of irreversibility, it seems reasonably certain the final cause of death involves the loss of vasomotor tone of the peripheral vessels and consequent stasis of blood.

AVIADO

Brun, C., Crone, C., Davidsen, H. G., Fabricus, J., Hansen, A. T., Lassen, N. A., and Munck, O.: Renal Blood Flow in Anuric Human Subject Determined by Use of Radioactive Krypton 85. Proc. Soc. Exper. Biol. & Med. **89:** 687 (Aug.–Sept.), 1955.

The renal blood flow in anuria cannot be measured with the direct Fick methods, since these depend on urine formation to determine the amount of test substance excreted. Inert gas diffusion technic using radioactive Krypton 85 was found to be reduced to approximately 20 per cent of normal values. Additional analysis of renal venous oxygen content afforded measurement of oxygen consumption of anuric kidney that was reduced to about 25 per cent. This confirms results obtained in anuric dogs and furthers the physiologic rule that blood flow to an organ is adjusted to its activity.

AVIADO

Covino, B. J., and Hegnauer, A. H.: Ventricular Excitability during Hypothermia and Rewarming in the Dog. Proc. Soc. Exper. Biol. & Med. **89:** 659 (Aug.–Sept.), 1955.

At normal body temperature, the ventricular myocardium of the pentobarbitalized dog exhibited an excitability recovery curve that was interrupted early in systole and late in systole by periods (dips) of lower thresholds than that obtained in immediately adjacent portions of the cycle. All portions of this excitability cycle suffer a progressive fall in threshold as body temperature is lowered to 25° under conditions of spontaneous respiration. The decrease in threshold is especially marked in early systole (and this is a reversible phenomenon), the normal excitability recovery curve being reestablished by rewarming to normal body temperature. The total refractory period and the ventricular conduction time are prolonged during cooling and return to normal during rewarming. No change in ventricular excitability is obtained during hypothermia, provided the pH of the blood is maintained at a normal level throughout the cooling process by artificial respiration.

AVIADO

Duff, R. S.: Effect of Adrenaline and Noradrenaline on Blood Vessels of the Hand before and after Sympathectomy. J. Physiol. **129:** 53 (July), 1955.

The effects on hand blood flow of infusing separately adrenaline and noradrenaline into the brachial artery have been measured in 10 patients by venous occlusion plethysmography. Before operation, noradrenaline caused more constriction than equal amount of adrenaline at all dose levels. After sympathectomy, the average constriction with adrenaline increased by about threefold and with noradrenaline by about twofold. Two of the present findings are contrary to Cannon's law of denervation that was based on animal experiments: (1) increased sensitivity was not demonstrable in 7 out of 13 denervated hands, and (2) ganglionectomy tended to cause no more sensitivity than preganglionic section.

AVIADO

Luisada, A. A., and Cardi, L.: Further Studies with Antifoaming Agents in Experimental Pulmonary Edema. Circulation Research **3:** 510 (Sept.), 1955.

The useful effect of ethyl alcohol vapor by inhalation previously demonstrated in alleviating experimental and clinical edema, was further confirmed by this new series of experiments. Several antifoaming agents were tested in preventing acute pulmonary edema caused by intravenous epinephrine in rabbits. Three agents were definitely beneficial, namely 10 per cent silicone in water, Freon, and ether alcohol. Mixtures of antifoaming agents did not show synergism. Since Freon might have systemic toxic effects, clinical trial should be limited to silicone aerosol and ether alcohol aerosol.

AVIADO

Page, E., and Real, J. D.: Interrelationships between Cardiac Effects of Ouabain, Hypocalcemia and Hyperkalemia. Circulation Research **3:** 501 (Sept.), 1955.

In dogs anesthetized with pentobarbital, ventricular arrhythmias induced by ouabain were consistently reverted to sinus rhythm by acute lowering of the serum calcium with disodium ethylenediamine tetra-acetic acid (EDTA). Lowering of the serum calcium in animals showing moderately advanced potassium effects in their electrocardiogram precipitated acute fatal potassium poisoning. This seemed to indicate increased cellular permeability to potassium as a primary consequence of acute hypocalcemia. Another form of antagonism was demonstrated by administering ouabain after initial hypocalcemia, which resulted in reversal of tachycardia and pulsus alternans in the face of persistent hypocalcemic tetany.

AVIADO

Raman, T. K., D'Baylis, V., and Pai, K. N.: Massive Pericardial Effusion. Indian Heart J. **7:** 34 (Jan.), 1955.

Six cases of massive pericardial effusion are described. The fluid was hemorrhagic in all cases except in 2. In these it was serofibrinous in the beginning and hemorrhagic later. The clinical, radiologic, and electrocardiographic diagnosis is discussed. *Mycobacterium tuberculosis* was isolated from the fluid in 1 case, and autopsy in another case showed giant cells with caseation.

In the majority of cases dyspnea of varying degrees was present. Aspiration of the fluid is the only method of relieving the dyspnea. Paracentesis of the pericardium may be done by any of the methods described. Shock, injury of the internal mammary vessels, puncture of the coronary vessels producing hemopericardium, laceration of the heart, and injury to pleura are the common complications. Pleural effusion or pneumothorax may occur.

BERNSTEIN

Zsótér, T., and Sebök, S.: Daily Variation of Antidiuretic Substance in the Blood Serum. Acta med. scandinav. **152:** 47 (July 29), 1955.

The determination of antidiuretic substance in the urine was studied by means of a biological technic, that of Kovács and Bachrach, in normal persons and in patients with heart disease. Some antidiuretic substance was present in the serum of 41 of 48 subjects. The antidiuretic substance was present in higher concentration at night than at noon, a feature present in both patients with heart failure and normal subjects. It was concluded from these observations that the nocturia observed in patients with congestive failure cannot be explained on the basis of a diurnal variation in the content of antidiuretic substances in the serum.

ROSENBAUM

Talley, R. W.: The Effect of Heparin on the Cerebral Blood Flow of Elderly State Hospital Patients. Am. J. M. Soc. **230:** 61 (July), 1955.

Because of its effect upon lipoprotein, chylomicrons, and neutral fat content of serum, heparin was administered to a group of 11 patients with cerebrovascular disease in order to determine its action on cerebral blood flow. Cerebral blood flow, oxygen utilization, and vascular resistance were measured by the nitrous oxide technic before and after the administration of 200 mg. of heparin, intravenously. All the patients manifested a reduction of cerebral blood flow and cerebral oxygen utilization, and an elevation of cerebral vascular resistance when compared to control patients. The administration of heparin did not produce any significant change in these values.

SHUMAN

Cogswell, R. C., Jr., and Browner, W. J.: Effects of Non-Voluntary, Electrically Stimulated, Muscular Activity on Pulse Rate, Blood Pressure and O_2 Uptake. J. Appl. Physiol. **8:** 19 (July), 1955.

This study was done to show that induced muscular activity produces changes similar to those invariably accompanying voluntary muscle contractions during exercise.

Ten healthy female subjects completed 10 45-minute exercise periods, each in the supine position, using electric stimulation applied to the rectus, lateral abdominal, gluteal, and lateral thigh muscles. Pulse rate, blood pressure, and O_2 consumption was measured during all periods of exercise and a control period before and after.

All subjects showed an increase in all functions. Pulse rate rose a mean of 17.2 beats/min., systolic blood pressure a mean of 12.2 mm. Hg, diastolic blood pressure a mean of 10.1 mm. Hg, and O_2 consumption a mean of 0.25 to 0.35 L./min. These increases were roughly proportional to the intensity of the electric stimulus and consequently to the muscle energy output.

It is concluded the electric stimulation of muscle contraction simulates voluntary, active physical exercise. Since no fatigue was noted, it is suggested that, short of actual biochemical failure, such fatigue is probably more psychogenic than "physiogenic" in origin.

WECHSLER

Gardier, R. W., and Woodbury, R. A.: The Renal Site of Action of Mercurial Diuretics. J. Pharmacol. & Exper. Therap. **114:** 453 (Aug.), 1955.

Conclusive evidence for the renal site of action of mercurials has not been provided. Most reports state that the site of sodium, chloride, and water diuresis is the proximal tubule. Others report the action on the distal tubule. Since the resorptive thresholds for the chloride and bicarbonate ions are interrelated in the proximal tubule, conclusive data may be expected by a study of the effect of mercurials upon the bicarbonate threshold of the proximal tubule.

In this study the proximal and distal tubular thresholds for bicarbonate reabsorption were determined under control conditions and in the presence of mercurial diuresis. All studies were accomplished on female dogs. Intravenous infusions of increasing concentrations of bicarbonate gradually elevated plasma bicarbonate levels. Creatinine clearances were determined as a measure of glomerular filtration rate. Plasma and urine pH, CO_2, Na, Cl, creatinine, and phosphate concentrations were measured. Mercaptomerin sodium was given intravenously in a dose of 5 mg. of mercury/Kg. body weight.

The mercurial caused a significant decrease in the bicarbonate threshold of the proximal tubule from 20.6 mEq./L. to 13.3 mEq./L. There was no significant change in the bicarbonate threshold of

the distal tubule, urine titratable acidity, and the increasing plasma pH's during the early part of bicarbonate infusion. In the mercurial treated group the pH fell during the later part of the bicarbonate infusion. Mercury lowered glomerular filtration rates and increased Na and Cl excretory rates approximately 20 to 30 times in the early part of the study. Later, this excretory rate decreased.

These results indicate that mercury affects the proximal tubules. The inhibition of Cl reabsorption started before the plasma bicarbonate reached the lowered threshold, and therefore there is no necessary relationship between this inhibition of bicarbonate reabsorption and the diuretic effect of mercurials. However, since the mechanism for bicarbonate reabsorption is thought to be similar in both the distal and proximal tubule, the lack of measured effect on the distal tubule in this study indicates that the reduction in chloride reabsorption is a result of proximal tubular action. The reduced glomerular filtration rate is thought to be caused by hemoconcentration.

WECHSLER

Roberts, J., Roy, B. B., Reilly, J., Garb, J., Riker, W. F., and Hoshimoto, K.: The Use of Certain Neuromuscular Blocking Drugs in an Analysis of Ventricular Irregularities Induced in the Cat. J. Pharmacol. & Exper. Therap. **114:** 279 (July), 1955.

The protection against induced ventricular arrhythmias provided by d-tubocurarine and Flaxedil has been ascribed to their vagolytic actions or to their direct effect on the myocardium. The present study is an attempt to clarify this problem.

Anesthetized cats were studied by means of carotid blood pressure measurements and electrocardiograms before, during, and after epinephrine and hydrocarbon-epinephrine induced ventricular arrhythmias. The effects of Flaxedil, d-tubocurarine, decamethonium, and the nonamethyl analogue of Flaxedil were studied.

Flaxedil averted the arrhythmias in more than one-half the animals treated. D-tubocurarine prevented the arrhythmias in all but 1 of the animals tested. Atropinization and bilateral cervical vagotomy also reduced the arrhythmias. The degree of protection afforded by either vagotomy or Flaxedil is less efficient than the effect of atropine or d-tubocurarine. Decamethonium and nonamethyl Flaxedil did not effect arrhythmia production. Nonamethyl Flaxedil has a curariform action on the neuromuscular junction but not the vagolytic action of Flaxedil. These results made it apparent that vagal blockade is the essential pharmacologic property in the antiarrhythmia actions of Flaxedil, d-tubocurarine, and atropine.

Inhalation of hydrocarbon blocked the protective effect of these drugs. Hydrocarbon inhalation replaces the depressant action of the vagus and therefore overrides the protective effect of these drugs whose antiarrhythmic effects depend on vagolysis. The increase of vagal tone and consequent increase in arrhythmias due to hydrocarbons such as petroleum ether are very important clinically. For cyclopropane the required concentrations more than encompass the anesthetic range. It is questionable whether the usual routine atropine premedication controls these vagal influences. In this regard the vagal blocking activity exhibited by Flaxedil in man may also prove useful.

These studies indicate that Flaxedil and d-tubocurarine diminish epinephrine-induced arrhythmias by virtue of their vagolytic actions and not by a direct effect on the myocardium. This inhibition is abolished if hydrocarbon inhalation is permitted. Decamethonium does not effect these epinephrine arrhythmias.

WECHSLER

Stroud, M. W., III, Lambertsen, C. J., Ewing, J. H., Kough, R. H., Gould, R. A., and Schmidt. C. F.: The Effects of Aminophylline and Meperidine Alone and in Combination on the Respiratory Response to Carbon Dioxide Inhalation. J. Pharmacol. & Exper. Therap., **114:** 461 (Aug.), 1955.

Aminophylline is clinically useful in the treatment of Cheyne-Stokes respiration. However, the mechanism of action of this drug is unknown. Previous work has shown that aminophylline constricts cerebral vessels, depresses brain oxygenation and fails to increase ventilation. These results are remarkable in that the direct action of aminophylline in smooth muscle of other vascular beds and upon bronchioles, intestine and ureters, is to produce relaxation. It has also been noted that arterial CO_2 tension fell, which suggests that respiration was stimulated by aminophylline.

This investigation studied the effects of aminophylline alone and with meperidine upon respiratory rate, depth and minute volume, and upon alveolar CO_2 tension, during the breathing of air at rest and during the inhalation of low concentrations of CO_2.

Intravenous aminophylline (3 mg./Kg. and 6 mg./Kg.) increased respiratory minute volume and lowered alveolar pCO_2 when the subjects breathed air or low concentrations of CO_2. The respiratory effect of 6 mg./Kg. dose was almost twice the 3 mg./Kg. dose. The concurrent administration of 6 mg./Kg. of aminophylline intravenously with 150 mg. of meperidine intramuscularly almost completely counteracted the depressant effect of the latter drug.

These results indicate that aminophylline causes a distinct increase in the respiratory response to CO_2 inhalation. This response probably represents alterations of the central response to CO_2 or second-

ary stimuli. Aminophylline made breathing easier at all concentrations of inspired CO_2. This may be related to cerebral stimulation, cardiac stimulation, or bronchodilatation.

WECHSLER

PHARMACOLOGY

Gardier, R. W., and Woodbury, R. A.: The Renal Site of Action of Mercurial Diuretics. J. Pharmacol. & Exper. Therap. **114:** 453 (Aug.), 1955.

The tubular thresholds for bicarbonate were determined in dogs under control conditions and in the presence of mercurial diuresis. Intravenous injection of mercaptomerin sodium lowered the bicarbonate threshold of the proximal tubule by approximately 35 per cent, but did not affect the distal tubule threshold. Since the mechanisms of bicarbonate reabsorption in the proximal and distal tubules appear to be similar, the renal site of action of an organic mercurial is in the proximal tubule. This strongly suggests that the reduction in chloride reabsorption is also a result of proximal tubular inhibition.

AVIADO

Woods, E. F., and Richardson, J. A.: A Survey of Agents Producing Cardiovascular Manifestations of Epinephrine Discharge. J. Pharmacol. & Exper. Therap. **114:** 445 (Aug.), 1955.

A wide variety of chemical substances acts on the adrenal medulla, either directly or indirectly, to modify the output of epinephrine. Intra-aortic injections of nicotine, potassium chloride, and calcium chloride produced epinephrine discharge as judged by increments in heart force, blood pressure, and heart rate of the anesthetized dog. These effects were not produced by intravenous injections of equal doses of the drugs, nor in adrenalectomized dogs. The ineffectiveness of histamine as an adrenal stimulant in the present experiments may be attributed to anesthesia that has been shown to reduce the responsiveness of the medulla to the stimulants. Moderate degrees of hypoxia did not significantly influence the adrenal responses.

AVIADO

Goldzier, S. E., Diamond, J., and Jezer, A.: Paroxysmal Tachycardia Due to Ephedrine Toxicity. J. Pediat. **47:** 599 (Nov.), 1955.

A 2½-year-old boy, while being treated for asthma with ephedrine, developed paroxysmal atrial tachycardia. The total dose administered over a period of 24 hours did not exceed 1 grain. Cardiac failure developed within 12 hours of the onset of the tachycardia. Eyeball pressure, carotid sinus pressure, and prostigmine administration did not abolish the disorder. Lanatoside C followed by eyeball pressure abolished the arrhythmia. Recovery was uneventful.

HARVEY

Fischer, M. H., Nüssen, W., and Stoboy, H.: Analysis of the Effect of Scilla on the Isolated Frog Heart. Ztschr. Kreislaufforsch. **44:** 684, 1955.

The electrocardiogram, the total plethysmogram of the heart, the "dynamogram" (combined aortic pressure and velocity curve), and the cardiac output (falling drop method) were registered synchronously in a frog heart perfused with Tyrode solution. Addition of Scilla extract ("Scilla-Perpurat"), 1:1000, usually did not influence the sinus rate, but sometimes caused an acceleration. The P-R interval was always shortened, and 2:1 A-V block disappeared if present previously. The amplitude of the plethysmogram increased with decrease of the diastolic volume; the dynamogram also became higher, and the heart output increased considerably. This effect was of short duration and was reversed by continuing the perfusion and by using higher concentrations.

LEPESCHKIN

Haley, T. J., and Weinberg, S. J.: Comparison of Strophanthin-K and Tryptamine-Strophanthidin after Intraventricular Injection in Unanesthetized Dogs. Proc. Soc. Exper. Biol. & Med. **89:** 345 (July), 1955.

A comparison was made of the effects produced by the intraventricular injection (through a previously inserted catheter) of Strophanthin-K and Tryptamine-Strophanthidin, a newly described compound with a typical digitalis action, on the isolated cat papillary muscle and on patients with atrial fibrillation.

Both drugs produced bradycardia and typical digitalis changes in the T-wave at low doses and manifestations of digitalis toxicity at higher doses. Some of the effects were not observed after much higher doses intravenously, thus indicating that the effects had their origin in the central nervous system. Anesthesia abolished these actions of the strophanthidin derivatives, indicating that anesthesia should be avoided in the study of centrally mediated drug effects.

MAXWELL

Rose, J. C., Freis, E. D., Hufnagel, C. A., and Massullo, E. A.: Effects of Epinephrine and Nor-Epinephrine in Dogs Studied with a Mechanical Left Ventricle. Demonstration of Active Vasoconstriction in the Lesser Circulation. Am. J. Physiol. **182:** 197 (July), 1955.

A mechanical pump to replace the left ventricle was the basic preparation in these experiments. It was possible to assess the effects of drugs upon the pulmonary artery and temporarily prevent the left atrial outflow from reaching the heart and systemic vessels. Epinephrine and norepinephrine constrict the pulmonary vessels, elevate pulmonary arterial pressure, and decrease pulmonary venous

flow. If the drugs are permitted to enter the systemic circulation, the rise in pulmonary arterial pressure is greater than when they are restricted to the lung alone.

OPPENHEIMER

Bengtson, E., and Karnell, J.: Parasympathetic Influences upon Cardiac Rhythm. Report of a Case. Cardiologia **27:** 120 (Fasc. 2), 1955.

Electrocardiographic studies are reported in the case of a 40-year-old man who complained of palpitation of 4 years' duration, with an otherwise negative past history. Physical findings were normal except for frequent premature beats that were atrial in origin. At times they caused bigeminy or were preceded by short periods of atrial flutter. This disturbance of rhythm was studied following exercise, carotid and bulbus pressure, during a Valsalva test, hyperventilation, in standing position, and after injection of atropine sulphate. Premature beats and paroxysms of atrial flutter became more frequent upon parasympathomimetic stimulation and disappeared transiently immediately after exercise and other procedures increasing sympathetic tone.

PICK

Hilton, J. G., Goodbody, M. F., Jr., and Kruesi, O. R.: The Effect of Prolonged Administration of Ammonium Chloride on the Blood Acid-Base Equilibrium of Geriatric Subjects. J. Am. Geriat. Soc. **3:** 679 (Sept.), 1955.

Uncoated ammonium chloride tablets in a dose of 1.5 mEq./Kg. body weight per day were given daily, from 4 to 14 days, to 2 groups of patients; namely, to 6 patients under 40 years of age, and to 6 patients over 65 years of age. Both groups were free of cardiovascular and renal disease. In the younger age group, blood acid-base equilibrium studies showed a complete compensation to the acid load by the fourth to seventh day (average 5.7 days). In the older age group, a state of metabolic acidosis resulted, which persisted as long as the acid load was administered. Thus, a diminution in the renal acidifying mechanism of geriatric subjects, aged 65 or over, is clearly present. No patient received more than 6 Gm. of uncoated ammonium chloride tablets daily.

RINZLER

McGinn, J. T., and Schluger, J.: Levarterenol Bitartrate (Levophed) in the Treatment of Cardiac Arrhythmias. Am. Heart J. **50:** 625 (Oct.), 1955.

Six cases of supraventricular paroxysmal tachycardia and 1 case of ventricular tachycardia are presented, in which the intravenous administration of levarterenol terminated the attack. In 1 case of atrial flutter the rate was slowed temporarily, but the abnormal rhythm persisted. Administration of the drug was only successful when it elevated the blood pressure to approximately normal levels.

It is suggested that levarterenol causes reversion to normal rhythm by elevating the blood pressure, thus stimulating receptors in the aorta and carotid sinus, which, in turn, causes reflex stimulation of the vagus. The profound vagal stimulation thus induced terminates the attack.

RINZLER

Lynch, P. R., Webber, D. L., and Oppenheimer, M. J.: Mephentermine as an Antifibrillatory Drug against Cyclopropane-Epinephrine Ventricular Fibrillation. Anesthesiology. **16:** 632 (July), 1955.

The antifibrillatory properties of mephentermine were investigated in dogs. Under cyclopropane anesthesia, mephentermine protected the animals against a predetermined surely lethal fibrillating dose of epinephrine. During the first half hour after induction of anesthesia, such protection was complete for mephentermine as well as ephedrine. Mephentermine, however, was found to have a greater protective effect than ephedrine in its shorter action and in the amount of epinephrine it could counteract. Although both drugs protected against fibrillation, they did not prevent the hypertension, tachycardia, and multifocal extrasystoles produced by subsequent administration of epinephrine. The other pressor drugs studied (N-methylmephentermine, l-norepinephrine, and l-epinephrine) had protective indices less than those of mephentermine or ephedrine. It was shown that neither anoxia nor sudden changes of CO_2 content were factors in these experiments. Respiration also was found to be stimulated by mephentermine and ephedrine. The possible mechanisms of the antifibrillatory action of mephentermine are discussed.

SAGALL

PHYSICAL SIGNS

Holldack, K.: Reduplication of the Second Heart Sound. Ztschr. Kreislaufforsch. **44:** 739, 1955.

The term "reduplication of the second sound" is often incorrectly used to designate the opening snap of the mitral valve, since in this case a new sound is added to the second sound. The term "reduplication" should also not be used to designate the wide splitting of the second sound such as is present in bundle-branch block, since in this case the second sound is not completely reduplicated, but only split into its aortic and pulmonary components. Since the term "reduplication" signifies a definite entity that is not often present, it is best not to use it at all in phonocardiography.

LEPESCHKIN

Schmidt-Voigt, J.: Final Remarks of Holldack on the Reduplication of the Second Heart Sound. Ztschr. Kreislaufforsch. **44:** 740, 1955.

The distinction between a split and a redupli-

cated second heart sound is important from purely descriptive, acoustic, and diagnostic standpoints. Since splitting of the second sound varies with respiration and is a normal variant, while reduplication is not influenced by respiration and is always pathologic. A revision and coordination of phonocardiographic nomenclature is urgently needed.

LEPESCHKIN

PHYSIOLOGY

Hercus, V. M., McDowall, R. J. S., and Mendel, D.: Sodium Exchanges in Cardiac Muscle. J. Physiol. **129:** 177 (July), 1955.

It was demonstrated quantitatively that sodium and potassium changes in the environment materially affect the activity of the isolated rat ventricle. The rat ventricle placed in a bath of normal Kreb's solution was shown to take up sodium and lose potassium. Stretching the muscle, or anoxia, greatly increases the uptake of sodium and also produces sustained damage to the sodium extrusion mechanism. The late failure of the muscle in the presence of oxygen after a short period of anoxia has been shown to be associated with an increased sodium uptake. This further supports the view that even short periods of anoxia, from which the preparation recovers temporarily, damage the mechanism for sodium extrusion.

AVIADO

Shaffer, A. B.: Observations on "Isometric" Contraction of the Atria in the Human Subject. J. Lab. & Clin. Med. **45:** 228 (Feb.), 1955.

Right atrial pressure pulses were obtained by cardiac catheterization in 3 patients who had widely different cardiac lesions, but showed, in common, the occurrence of virtually simultaneous contraction of the atria and ventricles, either as an intermittent phenomenon or for short periods. One case was a 12-year-old girl with severe pulmonic stenosis, an intact ventricular septum, and a patent foramen ovale. The second case was a 25-year-old man who had complete heart block (probably congenital) with a variety of pacemakers arising below the bifurcation of the common A-V bundle. The third case was a man of 52 years with mitral stenosis and a persistent atrial tachycardia with different grades of A-V block.

The pressure tracings of atrial contractions taken against closed A-V valves mostly showed markedly augmented "a" waves, which did not always represent isometric contraction of the atrium. For example, in the second case, when the atrium contracted very early in ventricular systole, the atrial systolic pressure was augmented by no more than 1 mm. Hg over that occurring in ventricular diastole even though the summit of the "a" wave occurred after the tricuspid valve closed. Thus, right atrial contraction against a closed tricuspid valve does not mean isometric contraction, presumably because reflux through the venae cavae can still occur, even though venous return must first be stopped and reversed. Only after ventricular ejection was well under way and pronounced, and led to an increased venous return to the right and left heart, did the "a" wave become markedly augmented. This case showed no significant caval closure reflexes.

In the third case, the right atrial systolic pressure against the closed tricuspid valve was 8 times the usual pressure and every second atrial contraction was isometric. Closed A-V valves and increased venous return constituted augmented afterloading of the atrium, resulting in the marked increase in atrial systolic pressure.

CORTELL

Liebau, G.: The Principles of Blood Flow in the Heart. Ztschr. Kreislaufforsch. **44:** 677, 1955.

The author attempts to find a teleologic reason why systole is much shorter than a diastole when both should be equal in duration to attain the greatest economy of work. One of the reasons could be a jet effect between atrium and ventricle, which facilitates unidirectional flow. Another is a hypothetical rectifying effect of the trabecular part of the ventricles on blood flow or the change in elasticity at the arteriovenous junction. A peristaltic contraction wave in the atrium or ventricle may cause unidirectional blood flow even without any valves; this takes place in the embryonic heart and in the heart of lower animals, and may also be of importance in human beings during emptying of the atria or in valvular insufficiency. These mechanisms produce a unidirectional effect only when the flow velocity is considerable, and this is the case only if systole is short.

LEPESCHKIN

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, NEW YORK 10, N. Y.

Telephone Gramercy 7-9170

APPLICATION DEADLINES SET FOR 1957 AHA RESEARCH SUPPORT

Applications for support of research to be undertaken during the fiscal year beginning July 1, 1957 are now being accepted by the Association. Persons seeking Established Investigatorships or Research Fellowships must submit their applications to the Association's Medical Director by September 15, 1956. Investigators who wish to apply for grants-in-aid must do so by November 1, 1956.

Following are descriptions of the various types of support for research in or related to the cardiovascular field maintained by the Association:

Established Investigatorships: These are awarded for periods of up to five years, subject to annual review, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. The initial stipend is $6,000 with an annual increment of $500.

Research Fellowships: These are awarded to individuals with doctoral degrees (M.D. or Ph.D.) for periods of one or two years to enable the recipient to obtain further research experience under the supervision of a senior investigator. The initial stipend ranges from $3,500 to $5,000 with the exact amount determined largely by the number of dependents supported by the investigator. There is a modest increase after one year.

Grants-in-Aid: These are awarded to experienced investigators to provide support for specific research projects. They are usually made for periods of one to three years in amounts generally not exceeding $10,000.

The American Heart Association maintains another and unique form of research support, the *Career Investigatorship*. This is given to a limited number of investigative scientists of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career Investigators are selected on the initiative of the Research Committee of the Association's Scientific Council, rather than by application.

Further information and application forms may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

The 32nd Annual Meeting and 29th annual Scientific Sessions of the Association will begin in Cincinnati on Friday evening, October 26, and continue through Wednesday, October 31.

Of greatest interest to the medical profession and to research investigators are the scientific programs which will be conducted from Friday evening through Monday, October 29. These programs will include presentation of papers based on original clinical and laboratory investigations, special lectures, panels and symposia, films and technical and scientific exhibits. The Cincinnati Music Hall will be the scene of most of these programs. Others will be at the Netherland Plaza Hotel, which will also serve as the American Heart Association headquarters.

The Scientific Sessions will be divided into general morning programs and simultaneous specialized afternoon programs. The opening session on Friday evening will be devoted to cardiac instrumentation.

Panels and Symposia

There will be four symposia or panel discussions during the Scientific Sessions. One is scheduled to inaugurate each of the three afternoon programs. Responsibility for arranging these has been assumed by Section on Clinical Cardiology of the Association. A symposium on "Cardiac Rehabilitation" will be conducted on Monday morning under the auspices of the Council on Community Service and Education.

Among the other highlights of the Scientific Sessions will be the George E. Brown and Lewis A. Conner Memorial Lectures on Saturday and Sunday Mornings. Two distinguished Medical Scientists, Hugh Montgomery, M.D., Philadelphia, and Jesse E. Edwards, M.D., Rochester, Minn., will deliver these lectures. The Council on Community Service and Education will conduct a luncheon meeting on Sunday followed by a program of interest to both professions and laymen. This luncheon and program will be at the Netherland Plaza Hotel, as will the luncheon meeting and subsequent scientific session of the Council on Rheumatic Fever and Congenital Heart Disease on Monday.

It is estimated that there will be facilities at the Cincinnati Music Hall for approximately 40 scientific exhibits and 88 technical exhibits. Commercial firms interested in presenting technical exhibits should address inquiries to Stephen K. Herlitz, exhibit manager, 280 Madison Avenue, New York. A special medical film program is also being arranged.

The Annual Dinner of the American Heart Association will be held on Sunday evening, October 28, at the Netherland Plaza.

ECG TEST BOOK ISSUED AS EDUCATIONAL AID

A two-volume *ECG Test Book* has been issued by the Association for the use of physicians both in individual study and in postgraduate courses. The work on electrocardiography is edited by Travis Winsor, M.D., Los Angeles.

Included in the testbook are 119 electrocardiograms, each of which is accompanied by a series of pertinent questions. There is also a section containing 230 general questions on electrocardiographic problems, and an appendix which includes a table of normal values. Answers to the questions, both those dealing with the specific electrocardiograms and those on cardiography, are contained in the second volume.

Copies of the *ECG Testbook* may be obtained from the Medical Division, American Heart Association, 44 East 23rd Street, New York 10, N. Y. The cost for the two-volume set is $5.00.

1955 HIGH BLOOD PRESSURE COUNCIL PROCEEDINGS AVAILABLE

The *Proceedings* of the 1955 Annual Meeting of the Association's Council for High Blood Pressure Research have been published. The 160-page volume is greatly expanded over the proceedings of meetings of the Council published in previous years. It contains all eight papers presented at the meeting in Cleveland last November, together with verbatim transcripts of the ensuing discussions. These papers include the following:

Integration of the Splanchnic Circulation in Systemic Hemodynamic Adjustments, Stanley E. Bradley, M.D., Department of Medicine of the College of Physicians and Surgeons, New York—a discussion of studies on determination of the capacity of the splanchnic vascular bed and of the role of the splanchnic circulation in cardiovascular adjustments.

The Pathogenesis of Experimental and Clinical Hypertensive Cardiovascular Disease, Arthur Grollman, M.D., Department of Experimental Medicine, Southwestern Medical School, Dallas—a presentation of the concept of renoprival hypertension.

Various Patterns of Blood Pressure Response to Autonomic Blockade: Implications Concerning the Interplay of Neurogenic and Humoral Factors in Control of Vascular Tone, Albert A. Brust, M.D. and Eugene B. Ferris, M.D., Department of Medicine, Emory University School of Medicine, Atlanta—a presentation of the thesis that the control of vascular tone may be on either a neurogenic or a humoral basis, or one in which both mechanisms are involved.

Essential and Abnormal Trace Metals in Cardiovascular Diseases, Henry A Schroeder, M.D. and H. Mitchell Perry, Jr., M.D., Hypertension Division, Department of Medicine, Washington University School of Medicine, St. Louis—a discussion of the possibility that the presence of certain "abnormal" trace metals and their relationship to essential trace metals may be factors in the pathogenesis of arterial hypertension and of atherosclerosis.

Experiments Bearing on the Role of the Limbic System in Cardiovascular Function: Conditioning and Reserpine Studies, Paul D. MacLean, M.D.,

Department of Physiology, Yale University School of Medicine, New Haven—a discussion of the effects of conditioning experiments and of reserpine on the nervous system of experimental animals and of its relation to the cardiovascular system.

Stress Mechanisms of Cephalic Brain Stem, H. W. Magoun, Ph.D., Department of Anatomy, School of Medicine, University of California, Los Angeles—a discussion of the potential routes through which internal and external stress can excite the cephalic portion of the brain stem, and relationships of these stresses to psychosomatic disease.

Bulbar Regulation of Cardiovascular Activity, S. C. Wang, M.D., Department of Physiology, College of Physicians and Surgeons, New York—a report on the effects of stimulation of various portions of the bulbar area on cardiovascular reflexes.

Central Action of Anti-Hypertensive Drugs, Jurg A. Schneider, M.D., Ciba Pharmaceutical Products, Inc., Summit, N. J.—a pharmacological approach to the study of drugs used in hypertension, and a discussion of the mode of action of the newer anti-hypertensive drugs.

The *Proceedings* may be obtained at a cost of $4.50 per copy from the American Heart Association, 44 East 23 Street, New York 10. A combination price of $7.50 has been set for the *Proceedings* volumes of the last four annual meetings, of the High Blood Pressure Research Council.

TWO INTERNATIONAL CONGRESSES OF CARDIOLOGY ON FALL CALENDAR

United States physicians and research scientists will be welcome at two international cardiologic congresses to be held abroad this Fall. These meetings are the Second European Congress of Cardiology in Stockholm, September 10–14, and the Fifth Inter-American Congress of Cardiology in Havana, November 11–17.

The American Heart Association will be officially represented at both meetings. The Association was also responsible for reviewing abstracts of papers for presentation at the Havana Congress submitted by U. S. research investigators. The Inter-American Congress actually will be the second of two major meetings of interest in the cardiovascular field to be held successively in Havana. The Latin American Congress of Angiology is scheduled for the Cuban capital beginning on November 8 and continuing through November 10.

Additional information on the Inter-American Congress of Cardiology may be obtained by addressing the Congress at Apartado 2108, Havana, Cuba. Registration fees may be paid by money order payable to Dr. Luis Ortega Verdes, Congress Treasurer. These fees are $25 for full registration, and $10 for associate registration which is available to members of the registrant's family. Application forms may be obtained from the American Heart Association.

Information on the European Congress may be obtained from Dr. Karl Erik Grewin, Secretary General, Second European Congress of Cardiology, Södersjukhuset, Stockholm, Sweden.

LAUNCH CARDIOVASCULAR DISEASE TRAINING PROGRAM IN CLEVELAND

A cardiovascular disease training program for young physicians has been inaugurated by Frank E. Bunts Educational Institute, teaching unit of the Cleveland Clinic, Cleveland, Ohio.

The program provides two-year traineeships oriented toward research and academic practice. The traineeships are available to physicians who have completed approved internships and at least two years of approved residency in either internal medicine or pediatrics. For eight months of the traineeship periods, the participants will study cardiovascular-renal disease in the Research Division of the Institute. The remaining 16 months will be divided equally between study of general cardiology and pediatric and surgical cardiology. These studies are undertaken in the Division of Medicine.

In each field, the trainee is responsible for a specific research project. Responsibility for the training in the Research Division is in the hands of Irvine H. Page, M.D., A. C. Corcoran, M.D., and Harriet Dustan, M.D. In the Division of Medicine, the responsibility is shared by A. Carlton Ernestene, M.D., William Proudfit, M.D., and F. Mason Sones, Jr., M.D.

Traineeships are to be provided for six physicians, three of whom were scheduled to begin their studies on July 1. The other three will be integrated into the program next year. Additional information may be obtained from the program's coordinator, Charles L. Leedham, M.D., Director of Education, Frank E. Bunts Educational Institute, 2020 East 93 Street, Cleveland 6, Ohio.

CARDIO-VIEWS KIT DEPICTS SECTIONS OF CV SYSTEM

A visual Cardio-Views kit on *The Cardiovascular System* is now available from the Association. The kit consists of 24 three-dimensional slides showing various parts of the heart including the valves, the coronary arteries, the aorta and the cerebrovascular system. It is designed for medical school and postgraduate teaching as well as for individual study by the physician.

The Cardiovascular System is the second kit in the Cardio-Views series. It is available from the American Heart Association, 44 East 23rd Street, New York 10, at a cost of $5.00. A special viewer, necessary for all Cardio-Views kits, is available for $1.25.

ECG COURSE PLANNED AT MICHAEL REESE

A course in electrocardiographic interpretation, directed by Louis M. Katz, M.D., is scheduled at the Michael Reese Hospital beginning on August 20 and continuing through September 1. Further information, including the lecture schedule, may be obtained from Mrs. Margaret Stern, Administrative Secretary, Cardiovascular Department, Michael Reese Hospital, 29th Street and Ellis Ave., Chicago 16, Ill.

MEETINGS CALENDAR

July 23–26: International Congress of Developmental Biology, Providence, R. I. Professor Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y.

July 27–31: International Symposium on the Cellular Basis of Differentiation, Providence, R. I. Professor Paul Weiss, Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y.

August 13–16: National Medical Association, New York. John T. Givens, M.D., 1108 Church St., Norfolk 10, Va.

August 29–September 2: Congress of the International Society for Blood Transfusion, Boston. Dr. J. Julliard, Secretary General of Society, 57 Boulévard L'Auteuil, Boulogne-sur-Seine, France.

September 3–9: Congress of the International Society of Hematology, Boston. Dr. S. Haberman, 3301 Junius St., Dallas, Tex.

September 6–8: American Association of Obstetricians and Gynecologists, Hot Springs, Va. F. R. Lock, Bowman Gray Medical School, Winston-Salem, N. C.

September 9–13: Congress of the International College of Surgeons (including Annual Congress of the U. S. and Canadian Sections), Chicago. Karl Meyer, M.D. 1516 Lake Shore Dr., Chicago, Ill.

September 9–14: International Congress of Clinical Chemistry, New York. Dr. John G. Reinhold, 711 Maloney Bldg., University of Pennsylvania, Philadelphia 4, Pa.

September 10–14: American Congress of Physical Medicine and Rehabilitation, Atlantic City. Frances Baker, M.D., One Tilton Ave., San Mateo, Calif.

September 17–20: American Hospital Association, Chicago. Edwin L. Crosby, 18 E. Division St., Chicago 10, Ill.

ABROAD

July 22–27: International Congress of Pediatrics, Copenhagen. Eighth International Congress of Pediatrics, Domus Medica, 12A Kristianiagade, Copenhagen, Denmark.

July 22–28: International Congress of Radiology, Mexico City. Dr. Jose Noriega, Secretary General of Congress, Tepic 126 (2e piso), Mexico, D.F. 7.

July 30–August 4: International Physiological Congress, Brussels. Professor J. J. Reuse, Faculté de Médicine et de Pharmacie, 115 Boulévard de Waterloo, Brussels, Belgium.

August 1–6: International Congress of Human Genetics, Copenhagen. University Institute for Human Genetics, Tagensvej 14, Copenhagen, Denmark.

August 19–23: International Congress on Diseases of the Chest, Cologne, Germany. Mr. M. Kornfeld, American College of Chest Physicians, 112 Chestnut St., Chicago 11.

August 20–24: International Congress of Physical Medicine, Copenhagen. Dr. Svend Clemnesen, Kommunehospitalet, Copenhagen, Denmark.

September 10–14: Second European Congress of Cardiology, Stockholm. Professor K. E. Grewin, Södersjukhuset, Stockholm, Sweden.

September 19–23: International Congress of Internal Medicine, Madrid. Professor Dr. Carlos Jumenez Diaz, Facultad de Medicina, Madrid, Spain.

CONTRIBUTORS TO THIS ISSUE

ALFRED J. BOLLET, M.D.

Clinical Investigations, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

GEORGE BRECHER, M.D.

Clinical Pathology Department, Clinical Center, National Institutes of Health, Bethesda, Md.

ROBERT A. BRUCE, M.D.

Associate Professor of Medicine and Head of Division of Cardiology, University of Washington; Attending Physician, King County Hospital; Consulting Cardiologist, Madigan Army General Hospital, Seattle Veterans Administration Hospital, U. S. Public Health Service Hospital, Seattle, Wash.

JOSEPH J. BUNIM, M.D.

Clinical Director, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

R. W. BURROUGHS, M.D.

Clinical Associate in Medicine, University of Washington; Member of Attending Staff, King County Hospital, Swedish Hospital, and Providence Hospital, Seattle, Wash.

LESLIE J. CERA, M.D., M.Sc., F.R.C.P. (C)

Demonstrator in Medicine, University of Manitoba Hospital; Director of Admission Services, Deer Lodge Veterans' Hospital, Winnipeg, Can.

JEROME F. CORDES, M.D.

Formerly Instructor and Research Associate in Internal Medicine, University of Michigan Medical School; presently practicing in Lansing, Mich.

VALENTINO DEFAZIO, M.D.

Life Insurance Medical Research Fellow 1953–1954; Instructor in Medicine, Wayne University College of Medicine; Assistant Physician, City of Detroit Receiving Hospital, Detroit, Mich.

MARY E. DEMPSEY, M.S.

Biochemist, Cardiovascular Disease Laboratory, Minneapolis Veterans Hospital; Instructor, Department of Medical Technology, University of Minnesota School of Medicine, Minneapolis, Minn.

JOHN W. FARQUHAR, M.D.

Formerly Resident in Medicine and Medical Fellow, Minneapolis Veterans Hospital and University of Minnesota School of Medicine, Minneapolis, Minn.; presently, National Heart Institute Research Fellow, University of California Hospitals, San Francisco, Calif.

NATHANIEL FINBY, M.D.

Instructor in Radiology, Cornell University Medical College, New York, N. Y.

ERNEST FRANK, PH.D.

Assistant Professor of Electrical Engineering, Moore School of Electrical Engineering, University of Pennsylvania; Research Assistant Professor of Electrical Engineering in Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

A. MCGEHEE HARVEY, M.D.

Professor of Medicine, Johns Hopkins University.

HARPER K. HELLEMS, M.D.

Associate Professor of Medicine, Wayne University College of Medicine; Attending Physician, City of Detroit Receiving Hospital; Director, Cardiovascular Research Laboratory, Department of Medicine, Wayne University College of Medicine and City of Detroit Receiving Hospital, Detroit, Mich.

T. F. HILBISH, M.D.

Chief, Diagnostic X-Ray Department, Clinical Center, National Institutes of Health, Bethesda, Md.

DON M. HOSIER, M.D.

Assistant Professor of Pediatrics, Ohio State University and Columbus Children's Hospital, Columbus, O.; Fellow in Cardiac Clinic, Harriet Lane Home, U. S. Children's Bureau Grant.

EDWARD J. HUTH, M.D.

Associate in Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

FRANKLIN D. JOHNSTON, M.D.

Professor of Internal Medicine, University of Michigan Medical School, Heart Station, University Hospital, Ann Arbor, Mich.

ANCEL KEYS, PH.D.

Director and Professor, Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

LEONARD LEIGHT, M.D.

Formerly, Instructor in Medicine and Research Associate, Wayne University College of Medicine; Junior Associate Physician, City of Detroit Receiving Hospital; currently, Assistant Professor of Medicine, University of Louisville College of Medicine, Louisville, Ky.

LENA A. LEWIS, PH.D.

Staff Member, Research Division, Cleveland Clinic, Cleveland, Ohio.

HENRY J. L. MARRIOTT, M.A., B.M. (OXON.)

Associate Professor of Medicine, University of Maryland School of Medicine; Chief, Electrocardiograph Department, Mercy Hospital, Baltimore, Md.

BENEDICT F. MASSELL, M.D.

Assistant Clinical Professor of Pediatrics, Harvard Medical School; Research Director, House of the Good Samaritan, Boston, Mass.

IRVINE H. PAGE, M.D.

Director, Research Division, Cleveland Clinic, Cleveland, Ohio.

H. MITCHELL PERRY, JR., M.D.

Instructor in Medicine, Department of Internal Medicine, Washington University School of Medicine; Established Investigator, American Heart Association, 1956; Assistant Physician, Barnes Hospital; Visiting Physician, Saint Louis City Hospital, Saint Louis, Mo.

JOHN L. PITTS, M.D.

Fellow in Cardiac Clinic Harriet Lane Home, U. S. Children's Bureau Grant, The Johns Hopkins Hospital, Baltimore, Md.

TIMOTHY J. REGAN, M.D.

U. S. Public Health Service Research Fellow of the National Heart Institute; Research Fellow in Medicine, Wayne University College of Medicine 1953–1955, Detroit, Mich.

ERNEST W. REYNOLDS, JR., M.D.

Instructor and Research Associate in Internal Medicine, University of Michigan Medical School, Heart Station, University Hospital, Ann Arbor, Mich.

SUJOY B. ROY, M.B., M.R.C.P., D.T.M. AND H. (EDIN.)

Fellow, the Massachusetts Heart Association; Assistant in Pediatrics, Harvard Medical School; Research Associate, House of the Good Samaritan, Boston, Mass.

HENRY A. SCHROEDER, M.D., F.A.C.P.

Associate Professor of Medicine and Director of Hypertension Division, Department of Internal Medicine, Washington University School of Medicine; Assistant Physician, Barnes Hospital; Consultant, Saint Louis City Hospital, Saint Louis, Mo.

EUGENE VAN SCOTT, M.D.

General Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

GEORGE E. SEIDEN, M.D.

Associate in Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

ERNST SIMONSON, M.D.

Associate Professor, Laboratory of Physiological Hygiene, University of Minnesota; Consultant in Electrocardiography, Veterans Administration Hospital, Mt. Sinai Hospital, University Hospital, Minneapolis, Minn.

RALPH E. SMITH, M.D.

Chief, Cardiovascular Disease Section, Minneapolis Veterans Hospital; Assistant Professor, Department of Internal Medicine, University of Minnesota School of Medicine, Minneapolis, Minn.

LEON SOKOLOFF, M.D.

Laboratory of Pathology and Toxicology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

LOUIS A. SOLOFF, M.D.

Clinical Professor of Medicine, Temple University Medical School and Hospital, Philadelphia, Pa.

RUSSELL D. SQUIRES, M.D.

Associate in Medicine and Assistant Professor of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

ISRAEL STEINBERG, M.D.

Assistant Clinical Professor of Medicine and Radiology, Cornell University Medical College, New York, N. Y.

NÁNDOR SZENT-GYÖRGYI, M.D.

Instructor in Medicine, Department of Medicine and Student Health Service, University of Chicago School of Medicine, Chicago, Ill.

FREDERICK N. TALMERS, M.D.

U. S. Public Health Service Research Fellow of the National Heart Institute; Research Fellow in Medicine, Wayne University College of Medicine 1952–1954; Instructor in Medicine, Wayne University College of Medicine; Junior Associate Physician, City of Detroit Receiving Hospital, Detroit, Mich.

HELEN B. TAUSSIG, M.D.

Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Physician in charge of Cardiac Clinic Harriet Lane Home, The Johns Hopkins Hospital, Baltimore, Md.

PARK W. WILLIS, III, M.D.

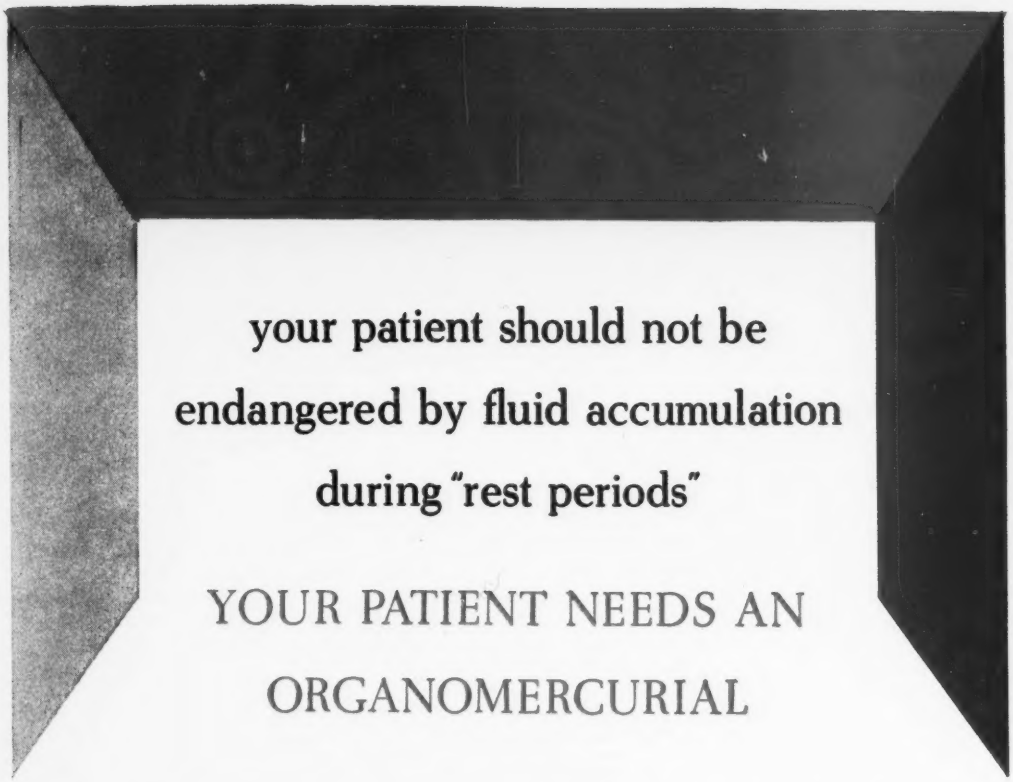
Instructor in Internal Medicine, University of Michigan Medical School, Heart Station, University Hospital, Ann Arbor, Mich.

IRVING S. WRIGHT, M.D.

Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, The New York Hospital, New York, N. Y.

JACOB ZATUCHNI, M.D.

Associate in Medicine, Temple University Medical School and Hospital; Associate in Medicine, Episcopal Hospital, Philadelphia, Pa.



your patient should not be endangered by fluid accumulation during "rest periods"

YOUR PATIENT NEEDS AN ORGANOMERCURIAL

When a diuretic must evoke acidosis to be effective, continued administration without dosage limitation results in refractoriness. Other diuretics may require interrupted dosage to avoid gastro-intestinal irritation.

But the sustained diuresis achieved by the organomercurials never necessitates routine "rest periods" because of their mode of action.

TABLET **NEOHYDRIN®**

BRAND OF CHLORMERODRIN (18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA EQUIVALENT TO 10 MG. OF NON-IONIC MERCURY IN EACH TABLET)

a standard for initial control of severe failure **MERCUHYDRIN® SODIUM**
BRAND OF MERALLURIDE INJECTION

01256

LAKESIDE

Circulation

JULY 1956
VOL. XIV NO. 1

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

EDITORIAL

AN EDITORIAL ON EDITORIALS...*Irving S. Wright and Herrman L. Blumgart* 1

THE NURTURE OF CARDIOLOGISTS: PRESIDENTIAL ADDRESS.....*Irvine H. Page* 3

RESULTS OF VALVULOTOMY FOR VALVULAR PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM: ANALYSIS OF SIXTY-NINE PATIENTS
Don M. Hosier, John L. Pitts and Helen B. Taussig 9

BLOOD PRESSURE STUDIES AMONG AMERICAN AND FOREIGN-BORN STUDENTS
Nándor Szent-Györgyi 17

THE ANGIOCARDIOGRAPHIC DIAGNOSIS OF LEFT ATRIAL THROMBOSIS
Louis A. Soloff and Jacob Zatuchni 25

EMETINE TOXICITY WITH ELECTROCARDIOGRAPHIC ABNORMALITIES..*Leslie J. Cera* 33

ATRIOVENTRICULAR SYNCHRONIZATION AND ACCROCHAGE.....*Henry J. L. Marriott* 38

COMPARISON OF LARGE AND SMALL DOSES OF HORMONES IN THE TREATMENT OF ACUTE RHEUMATIC CARDITIS.....*Sujoy B. Roy and Benedict F. Massell* 44

THE USE OF THE LEAD-FIELD CONCEPT IN THE DEVELOPMENT OF LEADS SATISFACTORY FOR VECTORCARDIOGRAPHY. I. THE SAGITTAL LEAD
Ernest W. Reynolds, Jr., Jerome F. Cordes, Park W. Willis, III and Franklin D. Johnston 48

HEREDITARY OBESITY: RELATION TO SERUM LIPOPROTEINS AND PROTEIN CONCENTRATIONS IN SWINE.....*Lena A. Lewis and Irvine H. Page* 55

THE RELATION OF CARDIOVASCULAR PHENOMENA TO METABOLIC CHANGES IN A PATIENT WITH CHRONIC HYPOKALEMIA
Edward J. Huth and Russell D. Squires 60

SIGNIFICANCE OF ABNORMAL PHASE II RESPONSE TO VALSALVA MANEUVER IN CARDIAC PATIENTS.....*Robert W. Burroughs and Robert A. Bruce* 72

THE EFFECT OF BETA SITOSTEROL ON THE SERUM LIPIDS OF YOUNG MEN WITH ARTERIOSCLEROTIC HEART DISEASE
John W. Farquhar, Ralph E. Smith and Mary E. Dempsey 77

COMPARISON OF LIMB AND PRECORDIAL VECTORCARDIOGRAPHIC SYSTEMS
Ernest Frank and George E. Seiden 83

CORONARY BLOOD FLOW, MYOCARDIAL OXYGEN CONSUMPTION, AND MYOCARDIAL METABOLISM IN NORMAL AND HYPERTHYROID HUMAN SUBJECTS
Leonard Leight, Valentino DeFazio, Frederick N. Talmers, Timothy J. Regan and Harper K. Hellems 90

THE EFFECT OF AGE ON MEAN SPATIAL QRS AND T VECTORS
Ernst Simonson and Ancel Keys 100

STUDIES ON THE CONTROL OF HYPERTENSION. VII. EFFECTS OF GANGLIONIC BLOCKADE COMBINED WITH HYDRALAZINE ON THE MALIGNANT STAGE COMPLICATED BY RENAL AZOTEMIA
H. Mitchell Perry, Jr. and Henry A. Schroeder 105

CLINICAL PROGRESS

CLINICAL MANIFESTATIONS OF THE UNPERFORATED AORTIC SINUS ANEURYSM
Israel Steinberg and Nathaniel Finby 115

CLINICAL CONFERENCE

SYSTEMIC LUPUS ERYTHEMATOSUS
Joseph J. Bunim, A. McGehee Harvey, Alfred J. Bollet, T. F. Hilbish, Eugene Van Scott, Leon Sokoloff and George Brecher 125

ABSTRACTS..... 135

AMERICAN HEART ASSOCIATION..... 154

CONTRIBUTORS TO THIS ISSUE..... 158